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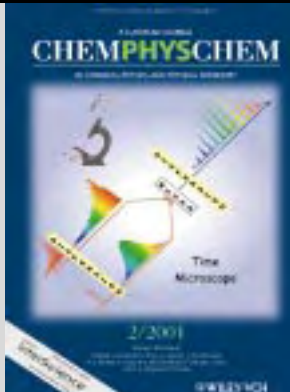
**2001
40/4**

Pages 635–804



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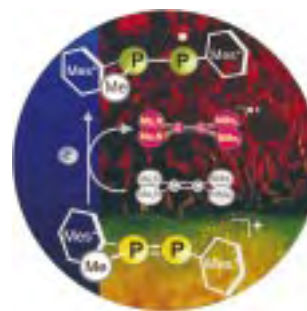
ChemPhysChem 2/2001 is bound
in this issue of *Angewandte Chemie*.



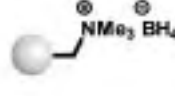
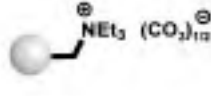
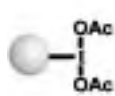
CHEMPHYSCHEM
A JOURNAL OF PHYSICAL CHEMISTRY
2/2001
Time
Microscope

COVER PICTURE

The cover picture shows the array of colors observed in the synthesis of the long-lived phosphorus radicals $[\text{Mes}^*\text{MeP}=\text{PMes}^*]^{\bullet}$ (**3**; $\text{Mes}^* = 2,4,6\text{-}t\text{Bu}_3\text{C}_6\text{H}_3$). These colors were obtained by layering a colorless solution of the electron-rich tetrakis(dimethylamino)ethylene (**2**) in acetonitrile onto a yellow solution of the phosphonium salt $[\text{Mes}^*\text{MeP}=\text{PMes}^*]^+[\text{O}_3\text{SCF}_3]^-$ (**1**) in acetonitrile. An immediate intense green color characteristic of solute **3** formed at the phase boundary. At the same time orange-red crystals of **3** appeared and deposited on the walls of the container. The red color denotes the formation of the radical cation $[(\text{Me}_2\text{N})_3\text{C}_2]^{\bullet+}$. More about this reaction, which has allowed the first isolation of diphosphanyl radicals, is described by Geoffroy, Grützmacher, and co-workers on page 723 ff.



A bright future for automated synthesis in solution: Functionalized polymers (see picture) have emerged as versatile synthetic tools for transforming reactants or removing by-products and impurities from solution, and have been employed successfully in multistep syntheses without the need for any further purification steps.



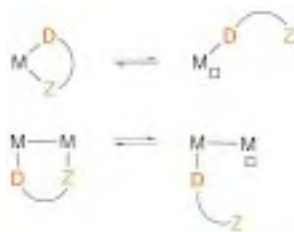
Angew. Chem. **2001**, *113*, 670–701

A. Kirschning,* H. Monenschein,
R. Wittenberg 650–679

Functionalized Polymers—Emerging
Versatile Tools for Solution-Phase
Chemistry and Automated Parallel
Synthesis

Keywords: automated synthesis •
combinatorial chemistry • functionalized
polymers • reagents

Ligand design—an essential part of synthetic chemistry! Ligands with different chemical functions (D and Z), such as hard and soft donors, are known as hybrid ligands. Such ligands can have hemilabile properties (see scheme) and find increasing use for tailoring the properties of metal complexes and designing new systems for molecular activation, homogeneous catalysis, functional materials, and small-molecule sensing. This review concentrates on multifunctional ligands with oxazoline moieties for which hemilabile properties were unknown until very recently.



Angew. Chem. **2001**, *113*, 702–722

P. Braunstein,* F. Naud* 680–699

Hemilability of Hybrid Ligands
and the Coordination Chemistry of
Oxazoline-Based Systems

Keywords: coordination chemistry •
homogeneous catalysis • hybrid ligands •
ligand design • sensors

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>

From Oligomers to Conducting Polymers of the Metal–Dinitrogen
Functionality

Heterogeneous Dinuclear Rhodium(II) Hydroformylation Catalysts—Per-
formance Evaluation and Silsesquioxane-Based Chemical Modeling

Formation of Super Wires of Clusters by Self-Assembly of Transition Metal
Cluster Anions with Metal Cations

Synthesis of Conformationally Locked Carbohydrates: A Skew-Boat Con-
formation of L-Iduronic Acid Governs the Antithrombotic Activity of
Heparin

Highly Efficient and Ultrafast Phototriggers for cAMP and cGMP by Using
Long-Wavelength UV/Vis Activation

Isolation and Structural Characterization of the Endohedral Fullerene
Sc₃N@C₇₈

E. Solari, J. Hesschenbrouck, ◆
R. Scopelliti, C. Floriani,* N. Re

M. Nowotny,* T. Maschmeyer, ◆
B. F. G. Johnson, P. Lahuerta,
J. M. Thomas, J. E. Davies

T. Nakajima, A. Ishiguro,
Y. Wakatsuki*

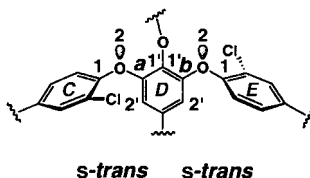
S. K. Das, J.-M. Mallet,
J. Esnault, P.-A. Driguez,
P. Duchaussoy, P. Sizun,
J.-P. Hèrault, J.-M. Herbert,
M. Petitou,* P. Sinaï*

V. Hagen,* J. Bendig, S. Frings,
T. Eckardt, S. Helm, D. Reuter,
U. B. Kaupp

M. M. Olmstead,
A. de Bettencourt-Dias,
J. C. Duchamp, S. Stevenson,
D. Marciu, H. C. Dorn*,
A. L. Balch*

Great confusion is often caused by the description of the configuration of molecules with numerous stereoelements, for example, complex natural products, with the CIP system. An example is given here (see picture), that of vancomycin, a glycopeptide antibiotic, whose different stereogenic units are described and a convention for the unambiguous notation for the stereogenic axes is proposed that is hoped will clarify future scientific publications.

Angew. Chem. **2001**, *113*, 723–726



K. C. Nicolaou,* C. N. C. Boddy,
J. S. Siegel* 701–704

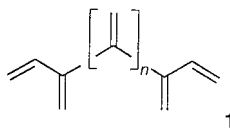
Does CIP Nomenclature Adequately
Handle Molecules with Multiple
Stereoelements? A Case Study of
Vancomycin and Cognates

Keywords: atropisomerism •
cycloisomerism • nomenclature •
stereochemistry • vancomycin

HIGHLIGHTS

Cross-conjugation is a widespread phenomenon in chemistry, especially in color chemistry. The simplest cross-conjugated organic compounds are the dendralenes with the general structure **1**. For decades these hydrocarbons only played a modest role in organic chemistry; however, the development of a general method of synthesis for **1** (up to $n = 4$) has led to the breakthrough which will enable a much more detailed investigation of the structural and chemical properties of these polyolefins.

Angew. Chem. **2001**, *113*, 727–729

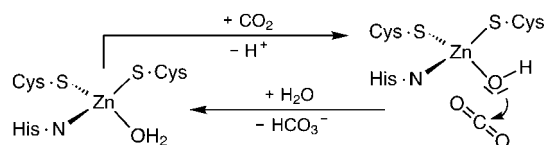


H. Hopf* 705–707

Dendralenes: The Breakthrough

Keywords: alkenes • C–C coupling •
conjugation • cycloaddition •
dendralenes

A positive biological function of the element cadmium has been established for the first time in a marine diatom which synthesizes a special cadmium carbonic anhydrase when there is a zinc deficiency. Also new is the finding that β -carbonic anhydrases of plants contain $\{Zn(N \cdot His)(S \cdot Cys)_2L\}$ centers ($L = OH_2$, $O_2C \cdot Asp$). The picture shows such a center and—greatly simplified—the probable mechanism of CO_2 hydration. It remains to be seen how closely analogous to this the cadmium center of the cadmium carbonic anhydrase is.



Angew. Chem. **2001**, *113*, 730–732

H. Strasdeit* 707–709

The First Cadmium-Specific Enzyme

Keywords: bioinorganic chemistry •
cadmium • enzymes • zinc

COMMUNICATIONS

New record size! The reaction of $Li[N(SiMe_3)_2]$ with a metastable solution of GaBr leads to good yields of $[Ga_{84}\{N(SiMe_3)_2\}_{20}]^{4-}$ (see picture), the largest Group 13 metalloid cluster that has been structurally characterized to date. On the basis of its highly symmetrical structure elements with predominantly covalent bonds, it is classified between the metalloid Al_{77} cluster and the fullerenes with respect to its bonding character.

Angew. Chem. **2001**, *113*, 734–737

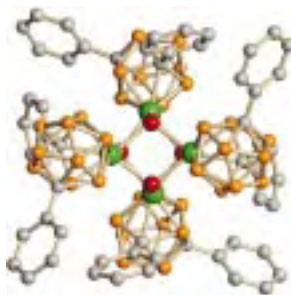


A. Schnepf, H. Schnöckel* 712–715

Synthesis and Structure of a $Ga_{84}R_{20}^{4-}$
Cluster—A Link between Metalloid
Clusters and Fullerenes?

Keywords: cluster compounds •
fullerenes • gallium • metalloid clusters •
metal–metal interactions

Monomer, dimer, trimer... now a tetrameric icosahedral metallocarborane $[\{\text{Rh}(\eta^5\text{-Ph}_2\text{C}_2\text{B}_9\text{H}_9)(\mu_3\text{-OH})\}_4]$ has been prepared as a minor by-product in the synthesis of $[\{1,8\text{-Ph}_2\text{-2-(1,2,3-}\eta^3\text{:5,6-}\eta^2\text{-C}_8\text{H}_{11}\text{)-closo-2,1,8-RhC}_2\text{B}_9\text{H}_9\}]$. The tetramer has approximate S_4 symmetry and a cubanelike $\{\text{Rh}(\text{OH})\}_4$ central core (see picture).



B. E. Hodson, D. Ellis, T. D. McGrath,
J. J. Monaghan, G. M. Rosair,
A. J. Welch * 715–717

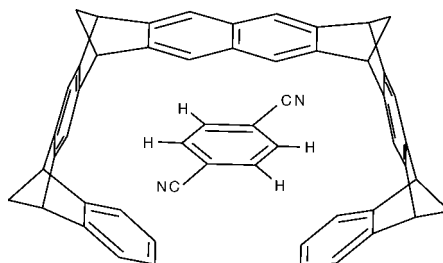
$[\{\text{Rh}(\eta^5\text{-Ph}_2\text{C}_2\text{B}_9\text{H}_9)(\mu_3\text{-OH})\}_4]$: A
Tetrameric Icosahedral Metallocarborane
Containing an $\{\text{Rh}(\text{OH})\}_4$ Cubane Cluster

Keywords: carboranes • cubanes •
metallocarboranes • rhodium

Angew. Chem. **2001**, *113*, 737–739



Together they are strong. The combination of fast MAS solid-state NMR experiments and ab initio calculations on ^1H chemical shifts allows the resolution and assignment of guest and host protons in a supramolecular complex (as shown here), provides information about motional processes, and identifies the specifics of intra- and intercomplex interactions.



S. P. Brown, T. Schaller, U. P. Seelbach,
F. Kozioł, C. Ochsenfeld, F.-G. Klärner,
H. W. Spiess * 717–720

Structure and Dynamics of the Host –
Guest Complex of a Molecular Tweezer:
Coupling Synthesis, Solid-State NMR,
and Quantum-Chemical Calculations

Keywords: ab initio calculations •
arenes • host–guest chemistry • NMR
spectroscopy • solid-state structures

Angew. Chem. **2001**, *113*, 740–743

The exchange of the methylene bridges in *p*-*t*Bu-calix[4]arene for sulfur produces a ligand seemingly perfectly suited for uranyl ions. Unlike most other metals, uranium does not bind to the four sulfur centers but is encapsulated by the ligand through binding to all four phenoxide groups (see picture). In contrast, calix[4]arene itself is dimensionally too restricted to function better than as a unidentate ligand for the uranyl ion.

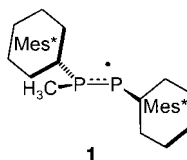


Z. Asfari, A. Bilyk, J. W. C. Dunlop,
A. K. Hall, J. M. Harrowfield,*
M. W. Hosseini, B. W. Skelton,
A. H. White 721–723

Subtleties with Sulfur: Calixarenes as
Uranophiles

Keywords: calixarenes • sulfur • uranium

Stable for at least one week below –30°C: crystals of **1**, the first highly persistent diphosphanyl radical, have been isolated and characterized. This phosphorus-centered radical exhibits hyperfine coupling whose anisotropy is considerably larger than that for well-established nitrogen radicals (hydrazyls, nitroxides). This feature is of potential interest for studies of fast molecular movements. Mes* = 2,4,6-*t*Bu₃C₆H₂.



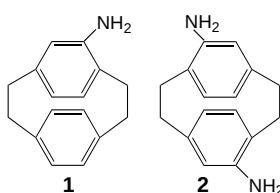
S. Loss, A. Magistrato, L. Cataldo,
S. Hoffmann, M. Geoffroy,*
U. Röhlsberger,
H. Grützmacher * 723–726

Isolation of a Highly Persistent
Diphosphanyl Radical: The Phosphorus
Analogue of a Hydrazyl

Keywords: density functional calculations • EPR spectroscopy • phosphorus • radicals • redox chemistry

Angew. Chem. **2001**, *113*, 749–751

Polymers based on functionalized [2.2]paracyclophanes are interesting interfaces for biomedical applications. A broader application of amino[2.2]-paracyclophanes such as **1** and **2** has hitherto been limited by the lack of facile syntheses. Their effective synthesis has now been achieved in a two-step procedure in high yields.



J. Lahann, H. Höcker,
R. Langer * 726–728

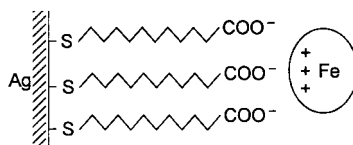
Synthesis of Amino[2.2]paracyclophanes—Beneficial Monomers for Bioactive Coating of Medical Implant Materials

Keywords: chemical vapor deposition • cyclophanes • immobilization • polymerization • superacidic systems

Angew. Chem. **2001**, *113*, 746–749

Time-resolved surface-enhanced resonance Raman spectroscopy

can selectively probe the molecular structure and dynamics of the active sites of redox proteins that are immobilized on self-assembled monolayers on Ag electrodes (see picture). As shown for the protein cytochrome *c*, this method is capable of analyzing complex interfacial processes in terms of electron transfer and non-Faradaic reactions.



D. H. Murgida,
P. Hildebrandt* 728–731

Active-Site Structure and Dynamics of Cytochrome *c* Immobilized on Self-Assembled Monolayers—A Time-Resolved Surface Enhanced Resonance Raman Spectroscopic Study

Keywords: electron transfer • heme proteins • immobilization • monolayers • Raman spectroscopy

Angew. Chem. **2001**, *113*, 751–754

The combination of two different biscatecholate ligands

with Ga^{III} ions gives rise to twelve different assemblies (shown schematically), which are all simultaneously present in solution. These were characterized by ESI-FTICR mass spectrometry and NMR spectroscopy. Even larger libraries are obtained by using an increasing number of components.



M. Ziegler, J. J. Miranda, U. N. Andersen,
D. W. Johnson, J. A. Leary,
K. N. Raymond* 733–736

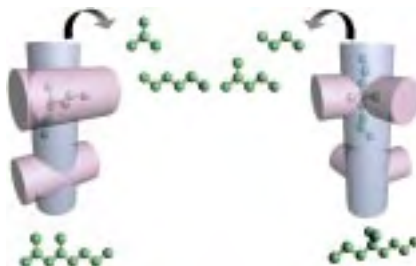
Combinatorial Libraries of Metal–Ligand Assemblies with an Encapsulated Guest Molecule

Keywords: cluster compounds • combinatorial chemistry • host–guest chemistry • self-assembly • supramolecular chemistry

Angew. Chem. **2001**, *113*, 755–758

A relatively simple reaction mechanism

for the conversion of alkanes in zeolites is obtained from molecular simulations by combining the thermodynamics with the diffusion and reaction barriers. The thermodynamics show which of the molecules will form in the zeolite, while the ultimate fate of a molecule, namely leave the zeolite or be converted (see schematic representation), depends on the relative heights of the Gibbs free energy barriers of diffusion and of subsequent reactions.



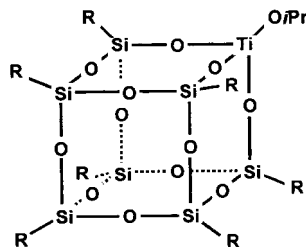
M. Schenk, B. Smit,* T. J. H. Vlucht,
T. L. M. Maesen 736–739

Shape Selectivity in Hydrocarbon Conversion

Keywords: alkanes • hydrocarbon conversion • molecular modeling • shape selectivity • zeolites

Angew. Chem. **2001**, *113*, 758–761

High-speed experimentation techniques have been applied in the synthesis and testing of silsesquioxane-based titanium catalysts (see picture) for the epoxidation of alkenes. Different solvents and organotrichlorosilanes were employed in the optimization of the hydrolytic condensation of silanes to open silsesquioxane structures. This new, fast, and simple synthesis route yields catalysts whose performance is comparable to the best known silsesquioxane-based titanium catalysts.



P. P. Pescarmona, J. C. van der Waal,
I. E. Maxwell, T. Maschmeyer* 740–743

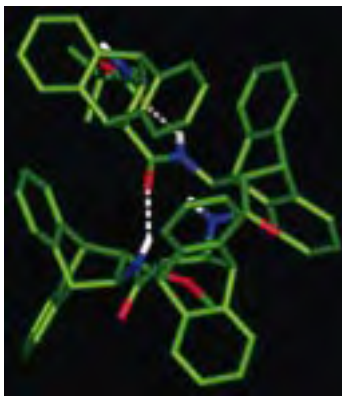
A New, Efficient Route to Titanium–Silsesquioxane Epoxidation Catalysts Developed by Using High-Speed Experimentation Techniques

Keywords: catalysts • epoxidation • high-throughput synthesis • silsesquioxanes • titanium

Angew. Chem. **2001**, *113*, 762–765

A twelve-membered hydrogen-bonded ring and the resulting helical structure (see picture) in the tetrapeptide and an eight-membered hydrogen-bonded ring in the dipeptide illustrate the structural consequences of the incorporation of the novel β -amino acid derived from the Diels–Alder adduct of anthracene and dimethyl fumarate.

Angew. Chem. **2001**, *113*, 765–767



J. D. Winkler,* E. L. Piatnitski,
J. Mehlmann, J. Kaspárec,
P. H. Axelsen* 743–745

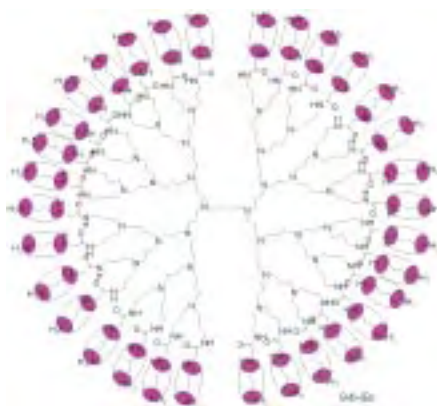
Design and Synthesis of Foldamers Based
on an Anthracene Diels–Alder Adduct

Keywords: amino acids • asymmetric
synthesis • conformation analysis •
peptidomimetics



Thirty-two molecular beads are threaded onto the terminal groups of a fourth-generation dendrimer (see picture). These pseudorotaxane-terminated dendrimers not only constitute a new class of topologically intriguing molecules but also provide a novel way of modifying dendrimer exteriors by noncovalent interactions.

Angew. Chem. **2001**, *113*, 769–771



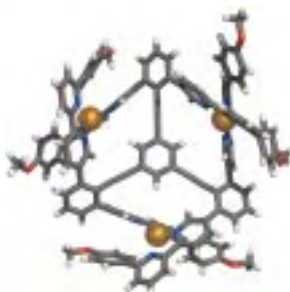
J. W. Lee, Y. H. Ko, S.-H. Park,
K. Yamaguchi, K. Kim* 746–749

Novel Pseudorotaxane-Terminated
Dendrimers: Supramolecular
Modification of Dendrimer Periphery

Keywords: dendrimers • noncovalent
interactions • rotaxanes • supramolecular
chemistry

The construction of molecules such as knots and links can be facilitated by using metal–ligand coordination complexes as template structures; however, the control of the stereochemistry by cooperative steric interactions among metal–ligand sites remains a challenge. A simple, but general, cantilever control mechanism is demonstrated here through the stereoselective synthesis of a trinuclear copper(I)-bipyridine triskelion (see picture).

Angew. Chem. **2001**, *113*, 771–773



C. R. Woods, M. Benaglia, S. Toyota,
K. Hardcastle, J. S. Siegel* 749–751

Trinuclear Copper(I)-bipyridine
Triskelion: Template/Bascule Control of
Coordination Complex Stereochemistry
in a Trefoil Knot Precursor

Keywords: coordination chemistry •
molecular design • stereochemistry •
supramolecular chemistry

Design principles in polynuclear coordination complexes have been based on the idea that metal ions would acquire donor atoms up to the metal's ligand field preference, and donor ligands, such as 1,10-phenanthroline, would not leave donor atoms uncoordinated to a metal ion. The geometry of the simple molecular grid formed from a series of 3,3'-biphenanthrolines complexed with Cu^{I} or Ag^{I} ions sets up a cleft that binds uncoordinated ligands through a combination of intercalation, solvation, and CH-to-N interactions (see picture).

Angew. Chem. **2001**, *113*, 773–776



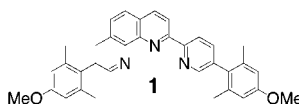
S. Toyota, C. R. Woods, M. Benaglia,
R. Haldimann, K. Wärnmark,
K. Hardcastle, J. S. Siegel* 751–754

Tetranuclear Copper(I)-Biphenanthroline
Gridwork: Violation of the Principle of
Maximal Donor Coordination Caused by
Intercalation and CH-to-N Forces

Keywords: coordination chemistry •
molecular design • stereochemistry •
supramolecular chemistry



As a hybrid of two aryl motifs, that is *p*-anisyl and mesityl, the 4-methoxy-2,6-dimethylphenyl or “manisyl” substituent offers possibilities for both further structural elaboration as well as enhancing the solubility of the heterocyclic ligands mentioned in the title. A highlight of this work lies in the ability of the manisyl group to endow specific members of this family such as **1** with high fluorescence quantum efficiency.



Angew. Chem. **2001**, *113*, 776–779

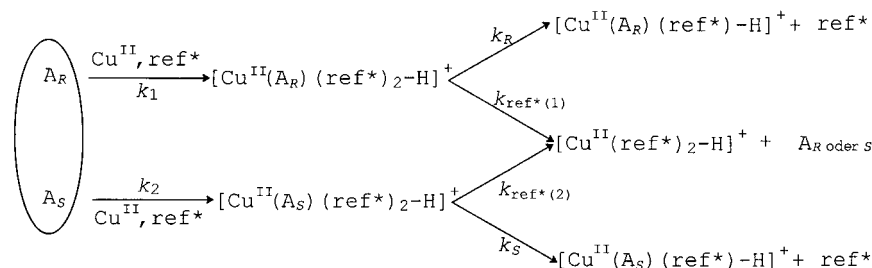
J. C. Loren, J. S. Siegel* 754–757

Synthesis and Fluorescence Properties of Manisyl-Substituted Terpyridine, Bipyridine, and Phenanthroline

Keywords: fluorescence • ligand design • N ligands • nitrogen heterocycles



Independent parallel ion/molecule reactions and fast dissociation have been used to quantify small enantiomeric excesses of dipeptides in a new mass-spectrometric method. The *ee* values are determined by simply mixing the analyte with CuCl₂ and a chiral reference compound (ref*) in aqueous methanol and observing the relative abundances of the diastereomeric cluster ions (see scheme).



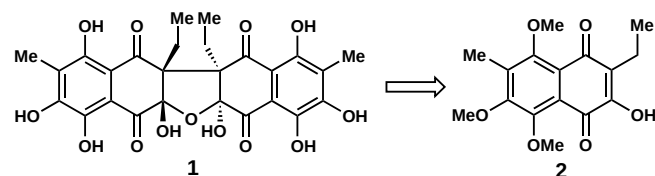
Angew. Chem. **2001**, *113*, 779–782

W. A. Tao, R. G. Cooks* 757–760

Parallel Reactions for Enantiomeric Quantification of Peptides by Mass Spectrometry

Keywords: chiral resolution • kinetics • mass spectrometry • peptides

A radical-based dimerization approach starting with naphthazarin **2** furnished the lichen-derived title compound **1** in racemic form. This cascade strategy, or a closely related variant of it, may not be too dissimilar to the pathway adopted by nature in the biosynthesis of this natural product which shows potent cytotoxic properties.



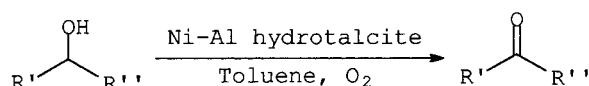
Angew. Chem. **2001**, *113*, 783–785

K. C. Nicolaou,* D. Gray 761–763

Total Synthesis of Hybocarpone

Keywords: natural products • oxidative coupling • photochemistry • quinones • total synthesis

NiO in association with aluminum oxide has been identified by temperature-programmed reduction as the active species in the Ni–Al hydrotalcite catalyst that oxidizes α -ketols as well as benzylic and allylic alcohols to their corresponding carbonyl compounds in oxygen in quantitative yields under mild reaction conditions (see scheme).



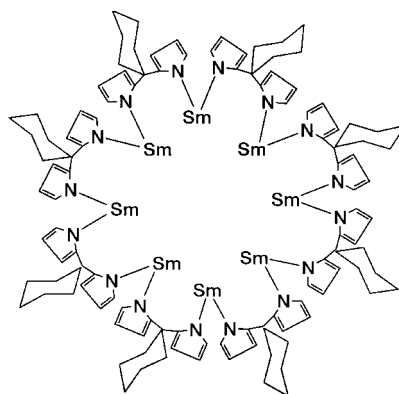
Angew. Chem. **2001**, *113*, 785–788

B. M. Choudary,* M. L. Kantam, A. Rahman, C. V. Reddy, K. K. Rao 763–766

The First Example of Activation of Molecular Oxygen by Nickel in Ni–Al Hydrotalcite: A Novel Protocol for the Selective Oxidation of Alcohols

Keywords: alcohols • hydrotalcites • oxidation • oxygen • reduction

Transamination reactions of $[(\text{Me}_3\text{Si})_2\text{N}]_2\text{Sm}(\text{thf})_2$ with the dianion of either 1,1-di-(α -pyrrolyl)-cyclohexane or diphenyl dipyrromethane led to the octanuclear complex shown in the picture and the hexanuclear complex $[[\text{Ph}_2\text{C}(\alpha\text{-C}_4\text{H}_3\text{N})_2]\text{Sm}]_6(\text{thf})_3$, respectively. Both clusters possess flat macrocyclic structures and react with dinitrogen to afford the corresponding isostructural tetranuclear dinitrogen complexes.



M. Ganesan, S. Gambarotta,*
G. P. A. Yap 766–769

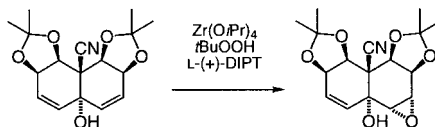
Highly Reactive Sm^{II} Macrocyclic
Clusters: Precursors to N_2 Reduction

Keywords: N ligands • N_2 complexes •
nitrogen fixation • samarium

Angew. Chem. **2001**, *113*, 788–791



Zirconium to the rescue! Eight contiguous chiral centers can be established with >95% *ee* in the key step of an asymmetric synthetic approach to the cores of certain *Celastraceae* sesquiterpenes (see scheme). The route required the development of a new zirconium-modified Sharpless asymmetric epoxidation instead of the traditional titanium version. DIPT = diisopropyl tartrate.



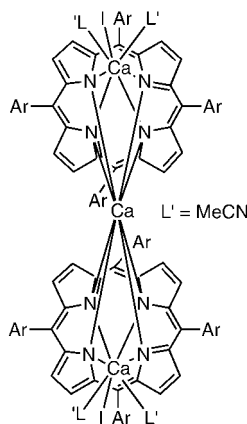
A. C. Spivey,* S. J. Woodhead,
M. Weston, B. I. Andrews 769–771

Enantioselective Desymmetrization of
meso-Decalin Diallylic Alcohols by a New
Zr-Based Sharpless AE Process: A Novel
Approach to the Asymmetric Synthesis of
Polyhydroxylated *Celastraceae*
Sesquiterpene Cores

Keywords: asymmetric catalysis •
desymmetrization • epoxidation •
natural products • zirconium

Angew. Chem. **2001**, *113*, 791–793

Unexpected salt-carrier properties are displayed by the calcium porphyrin presented here. The treatment of the free porphyrin with activated calcium metal gives a 1:1 complex in which the calcium ion is coordinatively unsaturated. Addition of $[\text{CaI}_2(\text{thf})]$ then results in the formation of a double-decker structure (see picture, Ar = *tert*-butylphenyl), which has been characterized by X-ray crystallographic analysis.



L. Bonomo, M.-L. Lehaire, E. Solari,
R. Scopelliti, C. Floriani* 771–774

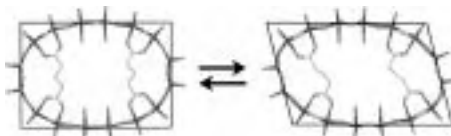
The First Crystalline Calcium Porphyrin
and Tetrakis(*tert*-butylphenyl)por-
phyrinato Calcium(II): Its Synthesis,
Structure, and Binding Properties
Towards Alkali and Alkaline Earth Metal
Salts

Keywords: calcium • NMR spectroscopy
• porphyrinoids • salt effect • structure
elucidation

Angew. Chem. **2001**, *113*, 793–796

**The largest discrete cyclic oxo-
thioanion**

$[\text{W}_{16}\text{S}_{16}\text{O}_{16}(\text{OH})_{16}(\text{H}_2\text{O})_4(\text{C}_5\text{H}_6\text{O}_4)_2]^{4-}$ was prepared by acido–basic self-condensation of the $[\text{W}_2\text{O}_2\text{S}_2]^{2+}$ building block in the presence of glutarate ions $[\text{C}_5\text{H}_6\text{O}_4]^{2-}$. The solid-state characterization (X-ray diffraction) revealed two conformations for the templated-ring which can be viewed as two snapshots of the dynamic of the wheel in solution (see picture). The ion was also characterized in aqueous solution by ^1H NMR and Raman spectroscopies.



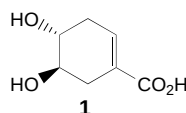
E. Cadot,* J. Marrot,
F. Sécheresse 774–777

$[\text{W}_{16}\text{S}_{16}\text{O}_{16}(\text{OH})_{16}(\text{H}_2\text{O})_4(\text{C}_5\text{H}_6\text{O}_4)_2]^{4-}$:
A Flexible, Pillared Oxothiotungstate
Wheel

Keywords: carboxylato complexes •
polyanions • sulfur • template synthesis •
tungsten

Angew. Chem. **2001**, *113*, 796–799

Competition feeding experiments performed in vivo have identified **1** as the true starter unit for the rapamycin polyketide synthase, and indicate its potential application for generating novel analogues of this clinically important immunosuppressant molecule.



P. A. S. Lowden, B. Wilkinson,
G. A. Böhm, S. Handa, H. G. Floss,
P. F. Leadlay, J. Staunton* 777–779

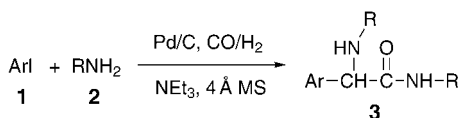
Origin and True Nature of the Starter Unit for the Rapamycin Polyketide Synthase

Keywords: biosynthesis • isotopic labeling • natural products • polyketides • reaction mechanisms

Angew. Chem. **2001**, *113*, 799–801



A new domino reaction sequence, a palladium-catalyzed double carbonylhydroamination, which involves double carbonylation, amine condensation, and hydrogenation from an aryl iodide (**1**), a primary amine (**2**), and synthetic gas has been realized as a novel synthetic means for the one-pot synthesis of α -amino amides (**3**).



Y.-S. Lin, H. Alper* 779–781

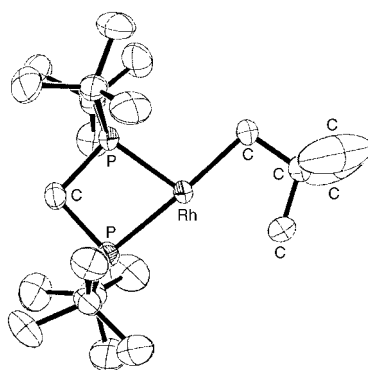
A Novel Approach for the One-Pot Preparation of α -Amino Amides by Pd-Catalyzed Double Carbonylhydroamination

Keywords: amination • amino amides • carbonylation • domino reactions • hydrogenation

Angew. Chem. **2001**, *113*, 801–803



γ -C–H agostic stabilization of the 14-electron metal center by a saturated hydrocarbon group characterizes the structure of the first neutral, three-coordinate alkylrhodium(I) complex $[(\kappa^2\text{-dtbpm})\text{RhNp}]$ (**1**; dtbpm = bis(di-*tert*-butylphosphanyl)methane, Np = neopentyl). Some of its reactions, for example, N_2 complexation and C–H bond activation, are reported.



H. Urtel, C. Meier, F. Eisenträger,
F. Rominger, J. P. Joschek,
P. Hofmann* 781–784

A Neutral Three-Coordinate Alkylrhodium(I) Complex: Stabilization of a 14-Electron Species by γ -C–H Agostic Interactions with a Saturated Hydrocarbon Group

Keywords: agostic interactions • C–H activation • density functional calculations • rhodium

Angew. Chem. **2001**, *113*, 803–806

Appreciable oxygen permeability at elevated temperatures (650–850°C) allows the well-known high-temperature superconductor $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ to be used as an oxygen separation membrane. Permeation of air through a $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ disk 1.2 mm thick gave an O_2 stream in which N_2 was barely detectable by gas chromatography. This technology may have potential applications in high-temperature oxygen-based industrial processes.

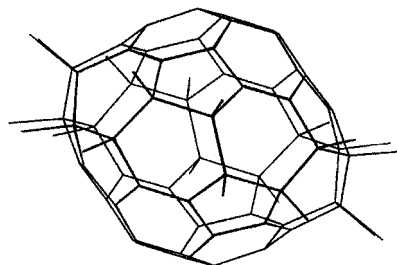
C.-s. Chen,* S. Ran, W. Liu, P.-h. Yang,
D.-k. Peng,
H. J. M. Bouwmeester 784–786

$\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ as an Oxygen Separation Membrane

Keywords: membranes • oxygen separation • perovskite phases • superconductors

Angew. Chem. **2001**, *113*, 806–808

Flattened poles and an expanded equator reminiscent of a spinning planet characterize the cage structure of D_{5d} $\text{C}_{60}\text{F}_{20}$ (“saturnene”, see picture) which is based on two dehydrocorannulene moieties bound together by a $(\text{CF})_{20}$ chain. $\text{C}_{60}\text{F}_{20}$ was isolated from the reaction of C_{60} with K_2PtF_6 in a vacuum at 470°C. The ^{19}F NMR spectrum shows a single line at $\delta = -132.8$. The unique structure of $\text{C}_{60}\text{F}_{20}$ suggests use as a synthon for derivatives having donor–acceptor properties.



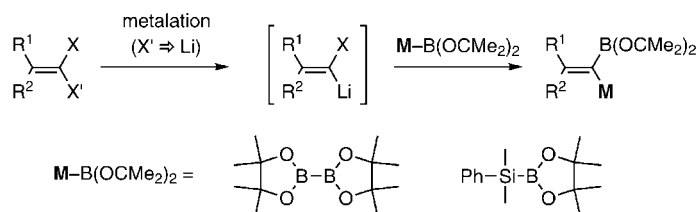
O. V. Boltalina,* V. Yu. Markov,
P. A. Troshin, A. D. Darwish, J. M. Street,
R. Taylor* 787–789

$\text{C}_{60}\text{F}_{20}$: “Saturnene”, an Extraordinary Squashed Fullerene

Keywords: fluorine • fullerenes • NMR spectroscopy • polyaddition

Angew. Chem. **2001**, *113*, 809–811

A 1,2-migration of a boryl or silyl group with inversion of configuration occurs in the reaction of alkylidene-type lithium carbenoids with diboron or silylborane derivatives to give the corresponding 1,1-diboryl- or 1-boryl-1-silylalkenes in good yields (see scheme).



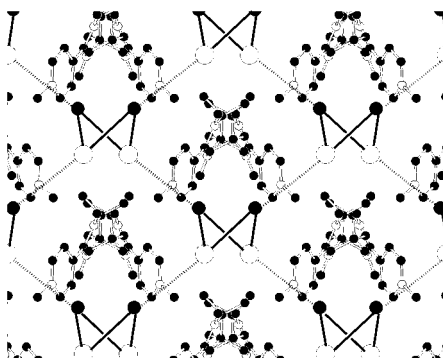
Angew. Chem. **2001**, *113*, 812–814

T. Hata, H. Kitagawa, H. Masai,
T. Kurahashi, M. Shimizu,*
T. Hiyama * 790–792

Geminal Difunctionalization of
Alkenylidene-Type Carbenoids by Using
Interelement Compounds

Keywords: borates • carbenoids •
metalations • palladium •
rearrangements

Stable free radicals can be trapped inside a three-dimensional (3D) inorganic network. The formation of a new type of mixed-metal oxalate $[\text{Mn}^{\text{II}}(\text{H}_2\text{O})\text{Cr}^{\text{III}}(\text{ox})_3]^-$ is induced by the presence of a cationic nitronyl nitroxide radical (rad^+). The figure shows a stylized view of the 3D network $\circ = \text{Mn}$, $\bullet = \text{Cr}$. This hybrid organic–inorganic compound behaves as an antiferromagnet at 6 K.



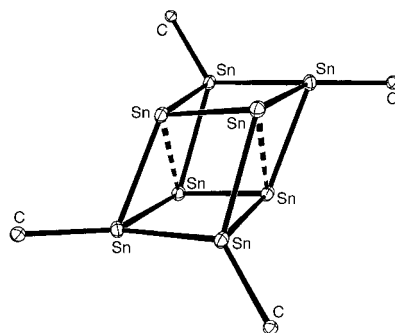
Angew. Chem. **2001**, *113*, 814–817

G. Ballester, E. Coronado,*
C. Giménez-Saiz,
F. M. Romero * 792–795

Nitroxide Radicals as Templating Agents
in the Synthesis of Magnets Based on
Three-Dimensional Oxalato-Bridged
Heterodimetallic Networks

Keywords: crystal engineering • host–
guest chemistry • magnetic properties •
organic–inorganic hybrid composites •
radicals

A distorted rhombic-prismatic arrangement, previously unobserved for a main group metal cluster, is present in $[\text{Sn}_8(2,6\text{-Mes}_2\text{C}_6\text{H}_3)_4]$ (see structure; only the *ipso*-C atoms of the ligands are shown), which was obtained by reduction of $[\{\text{Sn}(\mu\text{-Cl})(2,6\text{-Mes}_2\text{C}_6\text{H}_3)_2\}_2]$ with potassium in THF. Mes = 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2$.



Angew. Chem. **2001**, *113*, 818–819

B. E. Eichler, P. P. Power * 796–797

Synthesis and Characterization of
 $[\text{Sn}_8(2,6\text{-Mes}_2\text{C}_6\text{H}_3)_4]$ (Mes = 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2$): A Main Group Metal Cluster
with a Unique Structure

Keywords: C ligands • cluster com-
pounds • low-valent compounds •
terphenyls • tin



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

* Author to whom correspondence should be addressed



BOOKS

The Weak Hydrogen Bond

Gautam R. Desiraju, T. Steiner

J. Elguero 799

**Molecular and Supramolecular
Chemistry of Natural Products and
Their Model Compounds**

Jürgen-Hinrich Fuhrhop, C. Endisch

A. Davis 800

SERVICE

• VIPs	638	• Keywords	802
• Contents of <i>Chemistry—A European Journal</i>	649	• Authors	803
		• Preview	804
• Events	A19, A24	• Classifieds	A21

Issue 3, 2001 was published online on January 30, 2001.

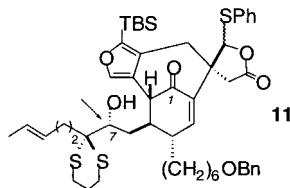
Don't forget all the Tables of Contents from 1995 onwards may be still found on the WWW under:
<http://www.angewandte.com>

CORRIGENDA

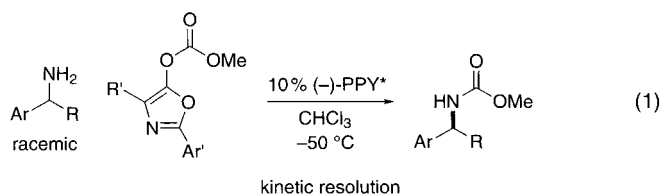
In the Communication by **S. Danishefsky et al.** in Issue 20, 2000, pp. 3652–3656 the acknowledgements should include the following: Z.-G.W. thanks the US Army for a postdoctoral fellowship (DAMD 7-97-1-7119).

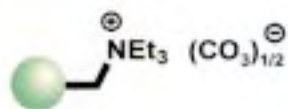
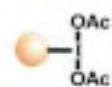
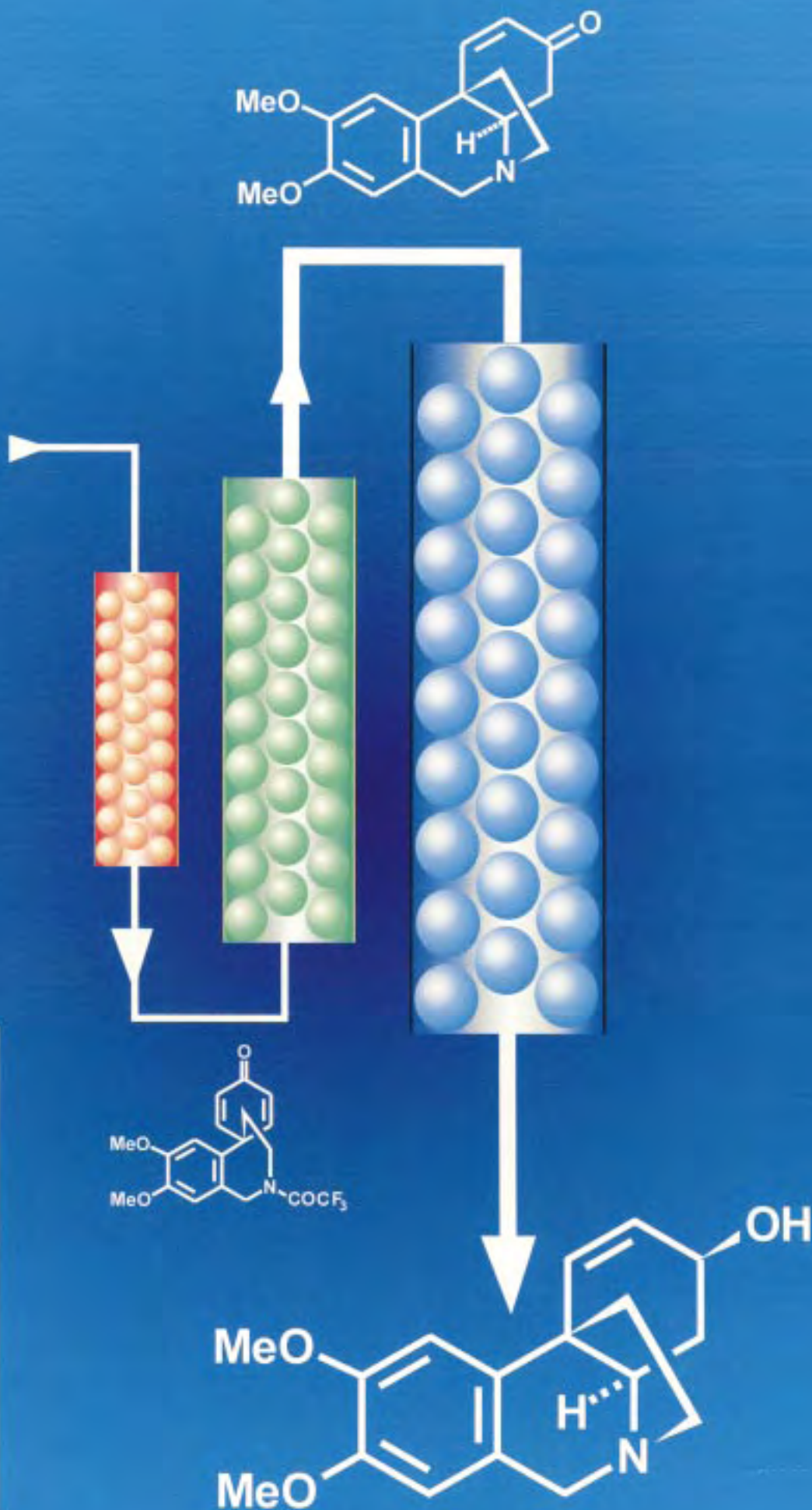
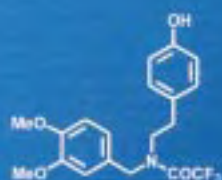
The $\pi^*(\text{FeO})$ orbitals in Scheme 2 of the Communication by **S. Shaik et al.** in Issue 21, 2000, pp. 3851–3855 were incorrectly described: they should be d_{xy} and d_{yz} instead of d_{xy} and d_{yz} .

The structural formula of compound **11** in the Communication by **S. Danishefsky et al.** Issue 24, 2000, pp. 4509–4511 contains two errors: a sulfur atom is missing in the dithiane ring and a hydroxyl group is wrongly placed at C1. The correct formula is given here.



The product in Equation (1) in the Communication by **G. C. Fu et al.** in Issue 1, 2001, pp. 234–236 contains one too many hydrogen atoms at the nitrogen atom. The correct version of the Equation is shown here.





Functionalized Polymers—Emerging Versatile Tools for Solution-Phase Chemistry and Automated Parallel Synthesis

Andreas Kirschning,* Holger Monenschein, and Rüdiger Wittenberg

As part of the dramatic changes associated with the need for preparing compound libraries in pharmaceutical and agrochemical research laboratories, industry searches for new technologies that allow for the automation of synthetic processes. Since the pioneering work by Merrifield polymeric supports have been identified to play a key role in this field however, polymer-assisted solution-phase synthesis which utilizes immobilized reagents and catalysts has only recently begun to flourish. Polymer-assisted solution-phase synthesis has various advantages over conventional solution-phase chemistry, such as the ease of separation of the supported species from a reaction mixture by filtration and washing, the opportunity to use an excess of the

reagent to force the reaction to completion without causing workup problems, and the adaptability to continuous-flow processes. Various strategies for employing functionalized polymers stoichiometrically have been developed. Apart from reagents that are covalently or ionically attached to the polymeric backbone and which are released into solution in the presence of a suitable substrate, scavenger reagents play an increasingly important role in purifying reaction mixtures. Employing functionalized polymers in solution-phase synthesis has been shown to be extremely useful in automated parallel synthesis and multistep sequences. So far, compound libraries containing as many as 88 members have been generated by using several

polymer-bound reagents one after another. Furthermore, it has been demonstrated that complex natural products like the alkaloids ($\pm$)-oxomaritidine and ($\pm$)-epimaritidine can be prepared by a sequence of five and six consecutive polymer-assisted steps, respectively, and the potent analgesic compound ($\pm$)-epibatidine in twelve linear steps ten of which are based on functionalized polymers. These developments reveal the great future prospects of polymer-assisted solution-phase synthesis.

Keywords: automated synthesis • combinatorial chemistry • functionalized polymers • reagents

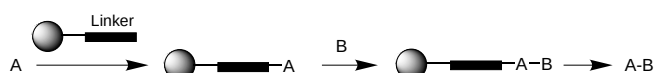
1. Introduction

Since the pioneering work by Merrifield^[1] polymer supports have become the subject of considerable and increasing interest as insoluble matrices in organic synthesis.^[2] This solid-phase technique revolutionized polypeptide and polynucleotide synthesis and, almost thirty years later, it set the stage for combinatorial chemistry. This conceptual revolution in organic synthesis was mainly governed by the need to generate rapidly libraries of compounds. In most cases, the development of new synthetic sequences on polymeric supports is regarded as the key for successfully generating these libraries (Scheme 1; method A).^[3]

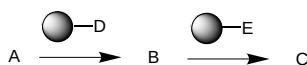
In the shadow of these dramatic changes, the utilization of functional polymers as reagents and catalysts has developed only sluggishly.^[4] In this process, the substrate does not remain attached to the solid support during a multistep synthesis until, in the final step, it is cleaved from the support, instead, the polymer-bound reagent or catalyst promotes a chemical transformation of a substrate which is present in solution. At first glance, it may be surprising that this approach has not been too popular, as this technique allows for the parallel solution-phase synthesis of organic compounds.^[5–7] In fact, this approach is very familiar to organic chemists, as reactions can be monitored using known analytical techniques like thin layer chromatography.^[8] In the seventies and eighties it was thought that the future of wide-scale use of polymeric reagents and catalysts lay in their adoption by industry for large-scale fine-chemical and pharmaceutical manufacturing. In fact, this restricted view hampered their use.^[9] The dramatic developments in pharmaceutical and agrochemical industries resulting in the need for compound library preparation has finally removed functionalized polymers from an

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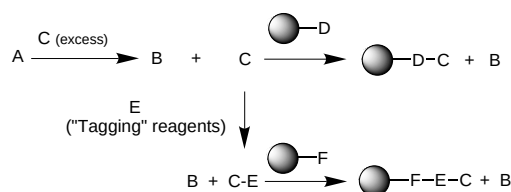
method A: Solid-phase synthesis



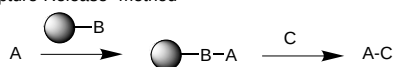
method B: Polymer-bound reagents and catalysts



method C: Polymer-bound scavenging reagents



method D: "Capture-Release" method



Scheme 1. Various uses of polymer supports in organic synthesis.

academic corner and helped them to be rediscovered for industrial applications.

This technique which in its most general form, and in this review, is termed polymer-assisted solution-phase synthesis has various advantages over conventional solution-phase

chemistry: 1) the ease of separation of the supported species, from a reaction mixture, by filtration and washing, 2) the possibility to use an excess of reagent to force the reaction to completion without causing workup problems, 3) reuse of a catalyst or of a supported reagent after regeneration, 4) the ease of adaptation to continuous-flow processes and hence use in automated synthesis, 5) the reduced toxicity and odor of supported species compared with low molecular weight unsupported analogues, 6) chemical differences, such as prolonged activity or altered selectivity of a catalyst in supported form compared with its soluble analogue.

Furthermore, polymer-assisted solution-phase syntheses shows advantages over Merrifield-type syntheses, these are summarized in Scheme 1 (methods B–D). Such methods are in fact much less demanding since polymer-supported reagents are used in only one reaction and, because of the excess of reagent usually employed, not every functional site needs to react. It has been demonstrated in numerous examples that, compared to solid-phase synthesis, the development time for new polymer-supported reagents and their applications is much shorter.

Nevertheless, the high loadings are still necessary in cases of reagents used stoichiometrically. With polymer-supported catalysts not every site needs to react and lower loadings are acceptable. The recovered catalyst is often available for immediate reuse. A discussion on functionalized polymers should also include a brief listing of obstacles associated with their use, particular in comparison to their soluble analogues,

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H. Monenschein

A. Kirschning

R. Wittenberg

Holger Monenschein was born 1972 in Hannover. He studied chemistry at the Technical University of Clausthal. There, he joined the group of A. Kirschning, starting his Ph.D. in 1998. His research interests involve the development and application of new polymer-supported reagents and, more recently, preparative natural product chemistry.

Rüdiger Wittenberg was born 1973 in Karlsruhe. He studied chemistry at the Technical University of Clausthal and the Universidad de Sevilla (Spain). In Clausthal, he joined the group of A. Kirschning, starting his Ph.D. in 1999. His research interests involve preparative natural product chemistry, namely the total synthesis of selected ansamycin antibiotics.

these are 1) higher costs, 2) lower reactivities because of diffusion limitations, 3) difficulty in structural analysis of the supported species, 4) the inability to separate polymer-bound impurities.

Until recently, polymer-bound reagents for stoichiometric use (Scheme 1; method B) have been the most important group of functionalized polymers. Now, additional techniques for polymer-assisted solution-phase synthesis are available. In this review the following terminology is used for these new functionalized polymers: polymer scavengers are resins which are added after a chemical reaction to remove excess reactants and by-products (Scheme 1; method C). The molecule to be removed can also be “tagged”, that is, derivatized and functionalized to facilitate its removal by a polymer scavenger. There is a subset of functionalized polymers which allow the “capturing” of a small molecule as an activated polymer intermediate. After washing to remove soluble by-products, this intermediate is subjected to a second transformation to “release” the product back into solution (Scheme 1; method D). As this hybrid technique basically combines the concept of solid-phase synthesis (method A) with the idea of polymer-supported reagents (method B) it will not be discussed here whereas the description and applications of methods B and C will be.

Lately, several excellent reviews have appeared indicating the increased interest in functionalized polymers and in the synthetic techniques associated with them. Most of these reviews introduced the reader to the preparation and properties of immobilized reagents,^[4] catalysts,^[8] and scavenging techniques.^[10] The true potential of functionalized polymers is reached when they are employed in multistep sequences and automated parallel syntheses leading to compound libraries. In multistep sequences polymer-supported reagents and catalysts along with the use of scavenging reagents and resin “capture–release” techniques can be mixed to generate ever more complex molecules. In an ideal synthesis of this kind, only filtration and washing is required for purification so that the process can be automated easily. Therefore, the discussion will focus on multistep sequences employing techniques B and C (Scheme 1).

As it becomes more and more evident that one key to the successful automation of organic synthesis is the development of altered or new polymeric backbones we include a brief discussion of various aspects in this field which are relevant for the functionalization of polymers. Recent trends in the rapidly developing field of inorganic supports will be covered as only a few examples of reagents attached to these promising supports have been published. To keep to a tractable length, polymer-supported catalysts are not covered in great detail mainly because they have not been employed in multistep sequences so far. The great initial hopes, particularly for polymer-bound transition metal catalysts, have, with few exceptions, not been fulfilled yet. One problem is that the transition metals are not bound irreversibly to the polymer support and transition metal complexes are not as stable as they were once thought to be. Still, we believe that the future prospects for polymer-anchored transition metal catalysts are bright, because they combine the best of both worlds: heterogenic and homogenic catalysis.

2. Polymer Supports

The attachment of a chemical functionality to a polymeric support has been realized by physical adsorption or by chemical bonding. The former technique is sometimes unsatisfactory, dissociation can occur too easily and hence this method is unsuitable for column or cyclic flow-reactor applications. Chemical attachment has been achieved through ionic or coordinative interactions, for example, with metal complexes and in an increasing number of cases by covalent bonding. The former mode of attachment is mainly found in ion-exchange resins and is highly attractive. These reagents are very easily regenerated, usually treatment with an excess of the ionic reactant is all that is required.

Two approaches exist for the preparation of functional polymers, the polymerization or copolymerization of monomers which carry the desired functionality, and the chemical modification of preformed polymers. It is mainly the second approach which has been exploited. In this respect, cross-linked poly(styrene-co-divinylbenzene) resins (1% or 2% cross-linking) are widely used as functionalized polymers because of their stability, reasonably high loading capacity ($>1 \text{ mmol g}^{-1}$), and good swelling characteristics. Furthermore, they are compatible with a variety of non-protic solvents and many functionalized analogues in particular based on ion exchange resins are commercially available.

The alternate concept, the polymerization of prefunctionalized monomers was extensively tested in the “early days” of polymer-assisted syntheses, for example, in the preparation of polymers containing pyridine^[11] or quinone^[12] residues, and benzaldehyde^[13] or phosphane^[14] functionalities. Although this approach demands that the synthetic organic chemist acquires a profound knowledge of polymers and polymerization, this strategy will acquire increasing importance because most supports employed today are still far from ideal (see Section 7).

For successfully designing new polymer-supported reagents, particularly in the context of combinatorial chemistry and automation, it is important to consider the properties and the role of the polymeric support.^[15, 16] In many cases, reactions carried out under homogeneous conditions are the same in terms of efficiency and selectivity as reactions of polymer-supported species. It must be remembered that up to 99% of functional groups of a polymer-supported system are within a polymer bead of diameter of about 100 μm . Thus, most of the reactants in solution have to enter the beads and react in a gel phase. The swelling of the polymers with organic solvents is one method of affording better access to the reactive sites of the polymer prior to its use. However, in this context it is important to recall that the extent of swelling decreases markedly as the percentage of cross-linking increases from 1% to 2% or more. The choice of reaction solvent is therefore crucial in polymer-supported reactions and the best solvent may not be the one commonly applied in the analogous reaction using low molecular mass reactants. The diffusion of the soluble substrate into the polymer beads is rate limiting and therefore, in some cases, can result in the supported reactant displaying a pronounced size selectivity.^[15–17] The selectivity arises because a more bulky molecule diffuses

more slowly to the reactive sites in the beads. Another effect that needs consideration occurs when the polarity of the microenvironment within the beads differs significantly from that of the solvent outside. This difference can either facilitate or prevent a low molecular mass reactant from approaching the active sites. For example, polymer-supported *N*-bromosuccinimide (NBS) shows a reactivity pattern with cumene in which the dehydrobromination reaction is more favored than in the solution reaction with NBS.^[18] The authors made the higher polarity in the beads around the active sites responsible for this behavior.^[15]

Generally, it is believed that attaching reactive species to a polymer support leads to site isolation, but in fact, many examples are known which clearly indicate that functional groups on a bead do interact with each other.^[15, 19] A typical loading of functional groups on a polystyrene-based support is around 1 mmol g⁻¹. This results in a concentration of reactive groups of around 0.33 mol dm⁻³ provided that the reaction solvent is able to swell the polymer by a factor of three. Indeed, site–site reactions can occur as, for example, was shown for polymer-supported Wittig reagents.^[20] One strategy to circumvent the ease of site–site interaction is to increase the percentage of cross-linking which is expected to reduce chain mobility. Noteworthy is that the supported substrate molecule can act as a flexible spacer group facilitating the side reactions caused by site–site interactions. In this respect, the strategy of polymer supported reagents (Scheme 1; methods B–D) clearly has advantages over the construction of molecules on a polymer support (Scheme 1; method A), the reagents are commonly small and thus site–site interactions in the bead are not particularly significant, and can be overcome simply by using an excess of the reagent without necessarily creating impurities in solution.

The accessibility of the active sites may be improved by using macroporous or macroreticular polymers.^[21] These polymers are usually prepared by suspension polymerization in the presence of a porogen to afford 20–40% cross-linked polystyrene beads. Typically, such beads have a rigid porous structure and normally do not swell in most organic solvents. Some commercial macroporous polymer supports, in particular certain anion-exchange resins, are ideally suited for making anions available for reactions in non-aqueous solvents.^[22] For example, the periodate form of such resins cleave diols in a wide range of different solvents such as ethanol, chloroform, diethyl ether, benzene, and even water.^[23] Another advantage of macroporous resins is their dimensional stability which makes them ideally suited for column applications where better solvent flow rates can be achieved than would be the case with gel polymers.

Contrary to the use of cross-linked polystyrenes, and of macropores, non-cross-linked polystyrene copolymer supports have been introduced to overcome the restricted access to active sites.^[24] These polymers are soluble in most organic solvents but precipitate in certain cooled solvents, for example, methanol.^[25, 26] This development is in line with the use of other soluble polymers and in particular soluble poly(ethylene glycol) (PEG)^[27] in polymer-supported synthesis. PEG was first studied by Bayer and Mutter and has recently been reintroduced by Janda and co-workers.^[28] In

many cases, these soluble supports behave like reactants in homogenous reactions.^[29] However, only limited use of reagents or catalysts attached to soluble polymers has been made, which can be ascribed to problems associated with their handling. PEG–ethers are highly hygroscopic and typically have low loading capacities (0.2 mmol g⁻¹). Often, large amounts of solvent are required to precipitate soluble polymers quantitatively. In particular the latter drawback makes them very difficult to use in automated parallel synthesis. An important new soluble polymer was recently reported by Frey and Haag, they described the controlled synthesis of well-defined hyperbranched polyglycerols^[30] which like related polymers^[31] have a very high loading capacity (4–8.8 mmol g⁻¹) and are superior to dendrimers in terms of preparative accessibility. As the authors point out, reagents or catalysts attached to soluble polymeric supports may be used conveniently in continuous reactors using membrane techniques (see also Outlook, Section 7).

3. Stoichiometric Polymer-Supported Reagents

Despite the dramatic increase in applications of, and enthusiasm for, polymer-supported reagents and catalysts (Scheme 1; method B) in solution-phase synthesis it is of note that the foundations of this technique were laid at the beginning of the seventies and lot of the credit for today's successes ought to go to the pioneers of that time. However, for reasons mentioned above these contributions came well ahead of the time when efficiently creating compound libraries was a prime goal. Therefore, stoichiometric polymer-supported reagents, including some important contributions from the early days are discussed.

Among these reagents, a clear classification is not always possible, for example, in many cases polymer-bound bases will not only act by deprotonating soluble organic substrates but are associated with further transformations such as the immobilization of counterions (see above) which initiates the nucleophilic substitution of alkyl halides and sulfonic esters or the Horner–Wadsworth–Emmons olefination of aldehydes. In addition, they have been employed widely as scavenging reagents (Scheme 1; method C) and for the “capture-release” technique (Scheme 1; method D). Herein, we pursued a classification based on the type of reaction rather than the nature of reagent.

3.1 Oxidations

For at least thirty years it has been known that oxidations can be promoted by polymer-bound reagents.^[32] Most of these oxidants were developed for the conversion of alcohols into carbonyl compounds. The number of polymers functionalized with ClCrO₃⁻, HCrO₄⁻, ClO⁻, and RuO₄⁻ ions is still increasing, the most prominent examples are listed in Table 1. Typically, these oxidants are attached by different N-heterocycles, or simple quaternary ammonium cations as in Amberlyst A-26, to the polymeric backbone. Also polymer-supported versions of the Swern oxidation^[33] (Table 1, entry 12) as

Table 1. Oxidation of alcohols.

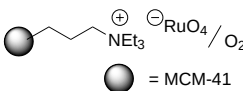
		$\text{R}-\text{CH}_2\text{OH} \xrightarrow{\text{polymer-bound oxidants}} \text{R}-\text{CHO}$			
Entry	Reagent/co-oxidant	Polymeric backbone ^[a]	No. ^[b]	Yield [%]	Ref.
1		PEI	10	73–98	[35]
2		PS (2% DVB) PS (2% EGDMA)	10	70–86 72–87	[36]
3		PS (2% DVB) PS (2% EGDMA)	10	75–90 80–90	[36]
4		PS (2% DVB) PS (2% EGDMA)	10	75–86 75–86	[36]
5		Amberlyst A-26	15	73–98	[37]
6		PS (2% DVB)	13	0–89	[38]
7		PS (2% DVB)	13	0–82	[38]
8		P-4VP (copolymer PS)	10	5–80	[39]
9		P-4VP	15	94–>99	[40, 41]
10		Amberlyst IR 27	10	54–95	[42]
11		Amberlyst A-26	7	56–95	[43]
12		PEG/PS	7	91–99	[44]
13		Amberlite XE-305	5	53–>99	[45]
14		IRA-900	5	60–98	[46]
15		Nylon 66	11	5–97	[47]
16		PS	8	66–95	[48]

[a] PEI = polyethyleneimine, PS = polystyrene, DVB = divinyl benzene, EGDMA = ethylene-glycol dimethylacrylate, PEG = poly(ethylene glycol), P-4VP = poly(4-vinylpyridine); [b] number of examples.

well as the Corey oxidation^[34] (Table 1, entry 13) were developed.

Suitable inorganic-based supports for chromium and other metal-based oxidants are silica gel and clays such as montmorillonite K10 (Table 2). These have served in numerous examples as excellent reagents for oxidizing alcohols of

Table 2. Oxidation of alcohols using silica-based oxidants.

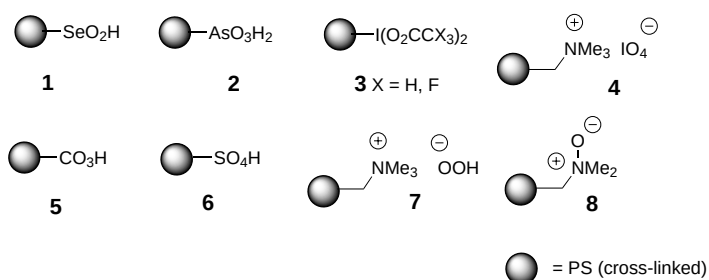
$\begin{array}{c} \text{R}^2 \\ \\ \text{R}^1-\text{CH}-\text{OR} \end{array} \xrightarrow{\text{oxidants absorbed on an inorganic support}} \begin{array}{c} \text{R}^2 \\ \\ \text{R}^1-\text{C} \end{array}$				
R	Oxidant	No. ^[a]	Yield [%]	Ref.
H	bis(trimethylsilyl)chromate/	22	71–99	[54]
SiMe ₃	SiO ₂ or	10	71–95	[49]
THP	Al ₂ O ₃	18	72–90	[60]
H	ammoniumchlorochromate/SiO ₂	16	70–95	[55]
H	chromium(vi)oxide/SiO ₂	7	46–85	[56]
H	chromium(vi)oxide/SiO ₂ /(SiMe ₃) ₂ O, microwave irradiation	10	72–99	[57]
SiMe ₃	iron(III)nitrate/montmorillonite K10	8	70–95	[50]
H	  = MCM-41	10	> 99	[58]
H	CrO ₂ (magtrieve)	7	61–95	[59]

[a] Number of examples.

various types to the corresponding carbonyl compounds. More recently, the direct oxidative deprotection of trimethylsilyl and THP-ethers (THP = tetrahydropyranyl) with Cr^{IV} oxides absorbed on silica gel or wet alumina^[49, 60] or with montmorillonite clay loaded with iron(III) nitrate^[50] was achieved, which increased the number for immobilized oxidants available. Similarly, oximes, semicarbazones, and *p*-nitrophenylhydrazones were oxidatively cleaved to their parent carbonyl compounds using different metal-based oxidants immobilized on inorganic supports.^[51]

Related to these applications montmorillonite clay,^[52] molecular sieves,^[61] bentonite,^[61] alumina,^[62] and in particular Kieselgur (82–97%)^[63] have served as solid supports for potassium permanganate. Only recently, Ley and co-workers disclosed an oxidant anchored to the macroporous inorganic support MCM-41 (Table 2).^[58] In the presence of oxygen, this immobilized catalyst is a very efficient oxidant for alcohol oxidation. Another remarkable oxidant, Magtrieve, created by Lee and Donald from Du Pont, is based on tetravalent CrO₂.^[59a] The oxide is able to convert alcohols as well as less active compounds like acetals and alkanes into aldehydes (Table 2).^[59] This reagent is produced in the commercial process for making magnetic-tape pigments but isolated prior to the reductive surface treatment. Since only the surface of the material is involved in the oxidation reaction the material remains ferromagnetic and can be readily removed by magnetic separation.

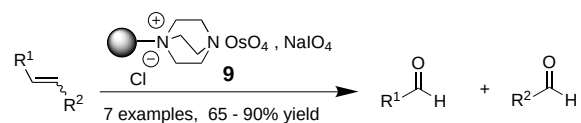
Furthermore, various polymer-anchored reagents **1–8** were developed for promoting diverse oxidations with functional groups other than alcohols. Thus, 1,2-*trans* diols (41–89%) are obtained from alkenes, and esters (71–98%) from the



corresponding ketones in a triphasic system composed of hydrogen peroxide, dichloromethane, and polymer-bound phenylselenenic acid (**1**).^[64] In the presence of *tert*-butyl hydroperoxide, **1** is able to effect selective oxidation of benzylic alcohols to the corresponding carbonyl species as well as the conversion of phenols to quinones.

A similar approach using arsenate polystyrenes **2** was reported by Jacobson et al.^[65] Oxidation of ketones by **2** in the presence of hydrogen peroxide affords the Baeyer–Villiger oxidation products, namely lactones, usually in very good yields. Polymer-supported α -oxidation of ketones has been achieved using the versatile oxidant poly(styrene(iodosobenzene diacetate)) **3** (X = H; for X = F see also Scheme 44).^[66, 67] Furthermore, **3** has been reported to promote oxidative 1,2-aryl migration of alkyl aryl ketones thus furnishing the corresponding α -aryl carboxylic esters.^[68, 69]

The periodate anion was immobilized, either on an ion-exchange resin to yield reagent **4**^[23, 70–72] or on inorganic supports,^[73] and was used in different organic solvents to promote oxidative cleavage of 1,2-diols. Furthermore, with **4**, quinones are transformed to quinones, sulfides are converted to sulfoxides, and triphenylphosphane is oxidized to triphenylphosphane oxide. Polymer-supported peracids **5** and **6** which are prepared from the parent polymer-bound carboxylic^[74] or sulfonic acids^[75] have been shown to oxidize thioethers and sulfoxides to the corresponding sulfones. In addition, alkenes are epoxidized and cyclic ketones are transformed to the ring-expanded lactones by means of the Baeyer–Villiger oxidation. Likewise, intermediate polymer-bound hydroperoxide **7** is able to promote epoxidation of alkenes including electron-deficient enones.^[76] Amine oxides **8** derived from aminated polystyrene resins are reported to selectively oxidize primary alkyl halides, in particular iodides, to the corresponding aldehydes.^[77] Various variants of polymer-supported osmium tetroxide have been disclosed. Although these reagents are used catalytically in the presence of cooxidants like trimethylamine-*N*-oxide (NMO) or *t*BuOOH^[78] one application should be mentioned here. Reagent **9** in combination with sodium periodate can be used to carry out an oxidative cleavage of alkenes leading to carbonyl compounds (Scheme 2).^[79] The continuous regener-



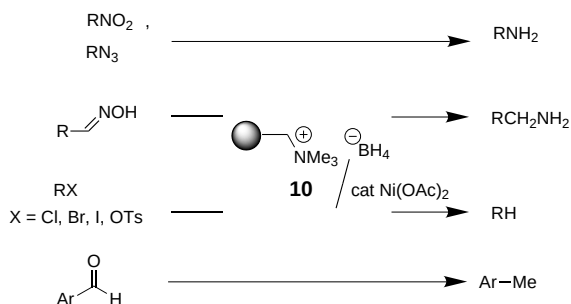
Scheme 2. Oxidative cleavage of alkenes by using polymer-supported osmium tetroxide.

ation of the polymer-bound osmium tetroxide by periodate allows the use of catalytic amounts of reagent **9**. Finally, the epoxidation of alkenes has been carried out using a polystyrene- or tentagel-anchored dioxirane and its analogues derived from trifluoromethyl ketones.^[80] The same reaction can be performed using the bromite anion attached to a macroporous anion-exchange resin (IRA-900), the active species can be regenerated electrochemically.^[81]

3.2 Reductions

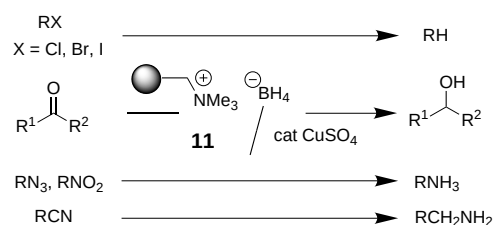
Polymeric supports are not only ideally suited for anchoring oxidants but have also been shown to immobilize reducing agents very effectively.^[82] The chemical modification of quaternary ammonium type resins, such as Amberlyst A-26, with NaBH₄^[83] and NaCNBH₃ (reported in the early seventies) gives highly efficient and chemoselective reducing agents.^[84] Recently, the polymeric backbones of these functionalized ion-exchange resins have been optimized.^[84b] In fact, these functionalized resins have been used in many organic transformations including the reduction of aldehydes and ketones,^[85] α,β -unsaturated carbonyl-compounds,^[86] benzyl and primary alkyl halides,^[87] and aliphatic acid chlorides.^[88] Even α,β -unsaturated cyanoacetates^[89] and nitroalkenes^[90] could be selectively reduced. Importantly, it was demonstrated that aryl azides and arylsulfonyl azides can be transformed to the corresponding aromatic amines and aryl sulfonamides, respectively, in up to 98% yield^[91] and even the reductive amination of aldehydes and ketones in weakly acidic alcohol solvents has been achieved using these polymer-supported hydrides.^[92] In Sections 5 and 6, many more applications of these reagents are mentioned.

An interesting modification of borohydride exchange resins (BER) is their combination with transition metal salts. Thus, cross-linked poly(4-vinylpyridine)-supported zinc borohydride was used to reduce aldehydes in high yields even in the presence of ketones.^[93] When Zr(BH₄)₄ is used instead,^[94] a polymer with enhanced reactivity is obtained which also reduces ketones, while conjugated double bonds are kept intact. The addition of a catalytic amount of nickel(II) acetate affords a very powerful and highly chemoselective^[95] functionalized polymer **10** which allows reduction of nitro^[96] and azido^[97] groups as well as aryloximes^[98] to the corresponding primary amines. Alkyl and aryl halides,^[99, 100] tosylates,^[99] and remarkably also benzaldehydes^[101] are converted into alkanes by **10** in moderate to excellent yields (Scheme 3).



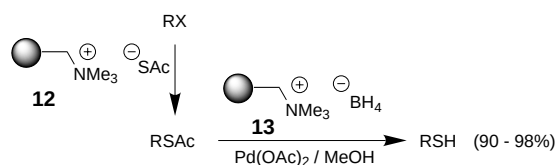
Scheme 3. Synthetic applications of BER and a catalytic amount of Ni(OAc)₂.

When borohydride is attached to Amberlite IRA 400 and treated with a catalytic amount of CuSO_4 a functionalized polymer **11** which is strong reducing towards different functional groups is obtained; these groups are listed in Scheme 4.^[102] Reagent **11** is particular useful for the reduction of alkyl halides including aryl iodides, azides, aldehydes, and ketones. Nitriles and particularly esters and amides are poor substrates. Alkenic double bonds when in conjugation with aryl or carbonyl groups are readily hydrogenated.



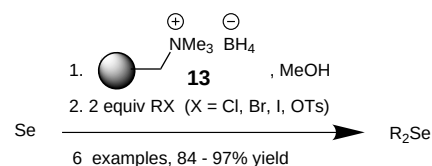
Scheme 4. Synthetic applications of BER and a catalytic amount of CuSO_4 .

Recently, the synthesis of thiols by palladium-catalyzed methanolysis of thioacetates was reported.^[103] Here reagent **13**, Amberlyst A-26 loaded with borohydride, served as the reductant. Prior to this step, alkyl halides were converted into the thioacetates using the appropriately loaded ion-exchange resin **12**. This two-step process can also be performed in a one-pot fashion (Scheme 5).^[103]



Scheme 5. A synthetic equivalent for polymer-supported SH^- .

Borohydride exchange resin (BER) in methanol is also able to reduce selenium, probably to give an immobilized selenide which reacts with alkyl halides or tosylates to afford dialkyl selenides in high yield without forming toxic hydrogen selenide and/or foul-smelling selenol (Scheme 6).^[104]

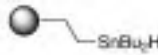
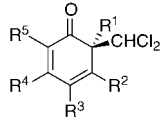
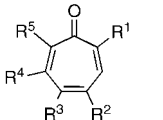
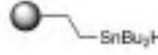
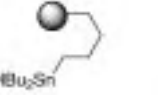


Scheme 6. BER-promoted preparation of dialkylselenides from selenium.

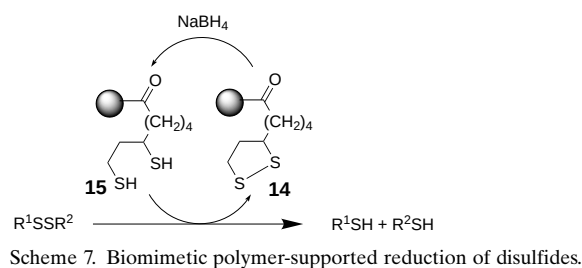
Another very important group of functionalized polymers with reductive properties are polymer-supported organotin reagents, especially tin hydrides.^[105] The development of these polymers was associated with the need, particularly for pharmaceutical applications, to improve separation techniques and prevent contamination by tin by-products. Therefore, a whole family of these reagents was introduced which mainly differ in the length of the aliphatic linker and the nature of the polymeric backbone. All of these polymer-supported tin hydrides have been employed for the reduction of sulfonic esters, xanthates, or alkyl halides, including tertiary bromides like adamantyl bromide (Table 3). However, in some cases the radical-induced cyclization of unsaturated organic halides is difficult to suppress (see also Table 6).

Finally, a biomimetic tool for the reduction of disulfides was developed by Gorecki and Patchornik (Scheme 7).^[112] Lipoic acid was coupled covalently to aminoethyl solid matrices. Treatment of this disulfide **14** with NaBH_4 gave the polymer-bound dithiol **15** which was shown to reduce oxidized glutathione and cystine.

Table 3. Reductions with polymer-supported tin hydrides.

Reagent	Polymeric backbone	Substrate	Product	No. ^[a]	Yield [%]	Ref.
1		PS (5–7% DVB)		1	> 99	[106]
2				12	29–99	[107]
3		PS	RX ^[b]	17	44–98	[108, 109]
4		Amberlite XE 305		1	93	[110]
5		Amberlite XE 305	3-iodo-5-cholesterene	1	60	[111]

[a] Number of examples; [b] X = Cl, Br, PhOC(S)O , MeSC(S)O .



3.3 Halogenations

Halogenation of organic compounds is a crucial step in the preparation of various synthetic intermediates or products. Therefore, it is not surprising that several polymer-bound halogenation reagents were established more than 20 years ago in the early days of functionalized polymers.^[11a, 18, 113, 114] Most of these reagents are based on ion-exchange resins^[115] often loaded with perbromide making them well suited for bromination reactions (Table 4). Commonly, these highly reactive reagents are stable and therefore can conveniently be stored. They perform 1,2-addition reactions to alkenes and alkynes^[116] as well as α -bromination of carbonyl compounds and acetals.^[116]

In contrast to the numerous examples of functionalized polymers that promote bromination, a general route for

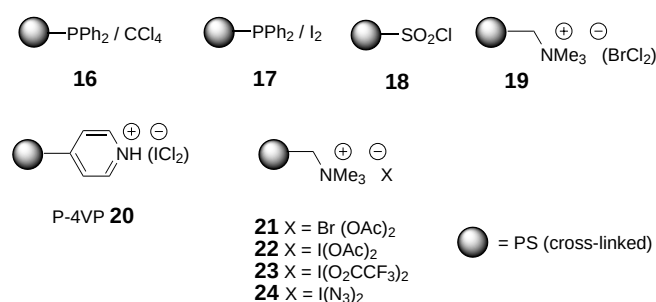
chlorination has not been worked out so far.^[122] Polymer-supported phosphane (poly-TPP; TPP = triphenylphosphane) in CCl_4 **16** is suited for the chlorination of primary alcohols to the corresponding alkyl chlorides under essentially neutral conditions.^[123, 124] The same reagent system and also a combination of poly-TPP and Cl_2 ^[14d, 125] is able to convert carboxylic acids into acid chlorides. The analogous reagent, poly-TPP and I_2 **17** has been used to transform alcohols, including N-protected β -amino alcohols, to the corresponding alkyl iodides.^[126] Furthermore, α -chlorination has been achieved using lithium diisopropylamide (LDA) and the immobilized chlorosulfonyl moiety **18**.^[127] Additionally, anion-exchange resins such as Amberlyst A-26 have been utilized for the preparation of polymer-bound interhalogen compounds.^[116] Reagents such as **19** perform chlorobromination of double- and also triple-bonds. Along this line, also polymer-bound dichloriodate(i) **20** was developed for the iodochlorination of alkenes and alkynes as well as monoiodination of arenes.^[128] The reagent system iodine and poly(styrene(iodo-doso)diacetate) **3** ($\text{X} = \text{H}$) also promotes efficient iodination of electron-rich aromatic compounds.^[68, 69]

Recently, new halogenate(i)-complexes were developed in our group^[129] which can conveniently be attached to anionic exchange resins. Reagents **21** – **24** promote Markovnikov-type 1,2-cohalogenation-like iodoacetoxylation of alkenes in most cases in a 1,2-*trans* mode.^[130] Furthermore, iodination of

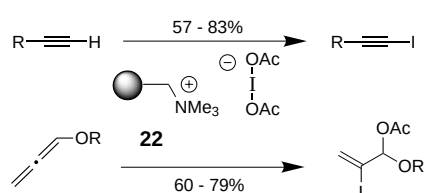
Table 4. Functionalized polymers for bromination.

Reagent	Polymeric backbone ^[a]	Substrate	Product	No. ^[b]	Yields [%]	Ref.
	Amberlyst A-162			9	60–98	[117]
	Amberlyst A-26	$\text{R}^1\text{CH}_2\text{C}(=\text{O})\text{R}^2$		12	70–97	[116]
		$\text{R}^1\text{CH}=\text{CH}\text{R}^2$				
	Amberlyst A-26	$\text{R}^1\text{CH}_2\text{C}(=\text{O})\text{R}^2$		5	55–78	[118]
	P-4VP			7	70–90	[119]
	P-4VP (copolymer with PS and DVB)	$\text{R}^1\text{CH}_2\text{C}(=\text{O})\text{R}^2$		4	80–>99	[11a]
		$\text{R}^1\text{CH}=\text{CH}\text{R}^2$		9	55–>99	[11a, 113]
				9	63–85	[120]
	PM5VTHT	$\text{R}^1\text{CH}_2\text{C}(=\text{O})\text{R}^2$		16	30–>99	[121]
		$\text{R}^1\text{CH}=\text{CH}\text{R}^2$				

[a] PM5VTHT = poly(4-methyl-5-vinylthiazol); [b] number of examples.

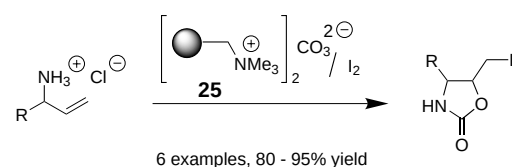


alkynes to the corresponding alkynyl iodides and chemo- and regioselective iodoacetoxylation of alkoxyallenes was achieved with functionalized resin **22** (Scheme 8). It is noteworthy that polymer-supported halogenate(I)-complex **24** is a stable and nonexplosive source for iodine azide, which indicates that on polymer supports a separation of active sites can be realized, thereby stabilizing a highly reactive species.



Scheme 8. Functionalization of alkynes and alkoxyallenes using polymer-bound iodate(I) complex **22**.^[130c]

Carboxylation and iodine-induced cyclization of allyl amines to iodomethyl-substituted oxazolidinones was achieved with the bisfunctionalized ion-exchange resin **25** composed of the basic carbonate anion which is complexed with molecular iodine (Scheme 9).^[131]



Scheme 9. Polymer-supported preparation of oxazolidinones from allyl amines.

A set of functionalized polymers was developed for the selective fluorination of organic compounds (Table 5). Primary and secondary alkyl fluorides are obtained from alkyl

Table 5. Polymer-supported fluorination.

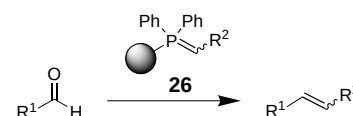
Reagent	Polymeric backbone	Substrate	Fluorinated Product	No. ^[a]	Yields [%]	Ref.
1	Amberlyst A-26	$\text{RX}^{[b]}$	RF	13	20–>99	[132]
2	P-4VP	ROH	RF	13	56–94	[133]
3	PS	Ph-CH=CH-Ph	Ph-CF2-CH2-Ph	6	85–96	[134]

[a] Number of examples; [b] X = Br, Cl, OM, OTs.

halides or organic sulfonates by using fluoride-loaded anion-exchange resin.^[132] Likewise, the combination of anhydrous hydrogen fluoride and poly-4-vinylpyridine (P-4VP) affords P-4VP poly(hydrogen fluoride) an efficient functionalized resin for the fluorination of alcohols and the hydrofluorination of alkenes and alkynes.^[133] Finally, polymeric aryldine(III) difluoride is able to fluorinate several phenyl-substituted olefins to their geminal difluorides after rearrangement.^[134]

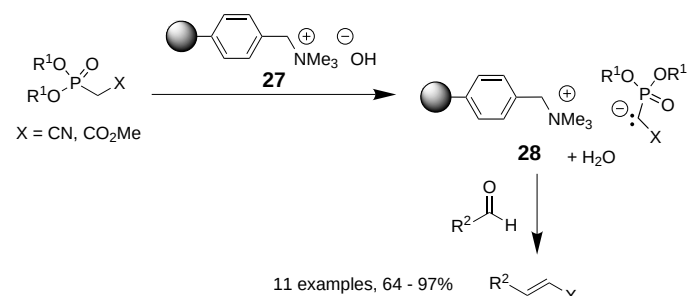
3.4 C–C Coupling reactions

The Wittig reaction and the organophosphorous chemistry derived from it^[135] are the best studied examples of carbon–carbon coupling reactions promoted by functionalized polymers. Commonly, polymer-bound phosphorous ylides **26** are employed, often giving yields and selectivities equal to those of the corresponding solution chemistry (Scheme 10).^[136] Highly cross-linked macroporous polystyrene supports (20% divinyl benzene (DVB)) has been shown to be particularly effective in this reaction.^[14b, 137, 138]



Scheme 10. Polymer-supported Wittig-olefinations. With R = alkyl: Z selectivity; with R = C(O)R²: E selectivity.

Polymer-supported Horner–Emmons olefination was first reported by Cainelli et al. (Scheme 11).^[139] The anion-ex-



Scheme 11. Polymer-supported Horner–Emmons olefination using ion pair reagents.

change resin Amberlyst A-26 (OH[−] form) **27** is sufficiently basic to deprotonate phosphonates thereby generating polymer-bound phosphonate anions **28**. These functionalized resins were further treated with carbonyl compounds to furnish the corresponding alkenes. A two-step extension of this work utilized Amberlyst A-15 (H⁺ form) prior to the olefination step. This ion-exchange resin promoted hydrolysis of a dioxolane affording the corresponding carbonyl compound which was further reacted to the corresponding alkene.

An alternative polymer-supported approach for the Horner–Emmons olefination was recently devised by Barrett et al. (Scheme 12).^[140] They performed a ring opening metathesis (ROMP) with 2-norbornenemethanol phosphonates, the polymerization afforded an immobilized phosphonate **29** which in acetonitrile and in the presence of Barton's base (*N*-tert-butyl-*N'*-*N''*-*N'''*-tetramethylguanidine) as well as a carbonyl compound exclusively afforded (*E*)-configured α,β -unsaturated esters.

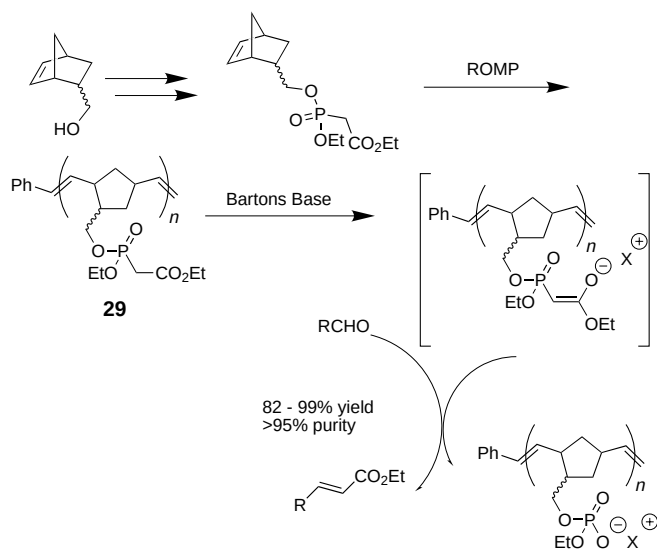
Likewise, sulfonium salts were also anchored to cross-linked polystyrene and sulfur ylides were generated, after use the sulfonium salts could be regenerated.^[141] These functionalized polymers have successfully been employed in reactions with carbonyl compounds leading to homologated oxiranes.

Polymer-bound organotin reagents are ideally suited for promoting free radical C–C coupling reactions (Table 6). Thus, allyl stannanes attached to soluble poly-

Table 6. C–C Coupling reactions using polymer-bound organotin reagents.

Reagent	Polymeric support	Substrate	C–C coupling product	Yield [%]	Ref.
	PS (non-cross-linked)			66	[142]
	PS	$\text{CH}_2=\text{CHCN} + \text{R-X}$ X = Br, I	$\text{R-CH}_2\text{CH}_2\text{CN}$	10–93	[106a, 110, 143]
	PS			89	[144]
	PS	$\text{R}^1\text{C}\equiv\text{C}\text{R}^2 + \text{R}^3\text{I}$		66–78	[144]
	PS	R^1X	R^1R	51–96	[145]

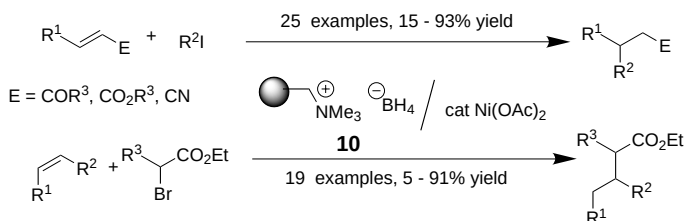
[a] AIBN = azobisisobutyronitrile.


 Scheme 12. Polymer-bound phosphonate **29** generated by ring-opening metathesis (ROMP).

meric supports, namely non-cross-linked polystyrene, allow allyl transfer onto organohalides (five examples; 50–73% yield).^[142] Accordingly, polymer-attached distannanes are able to promote cyclization of unsaturated alkylhalides as well as radical addition of alkylhalides to alkynes.^[144] When polymer-anchored tin reagents are loaded with transferable functional groups like vinyl or aryl substituents (R) the palladium-catalyzed Stille reaction becomes feasible.^[145]

Nickel(II) boride BER **10** has proven to be a substitute for polymer-bound tributyltin hydride (see also Scheme 3), because it promotes the radical addition of alkyl iodides to

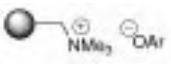
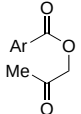
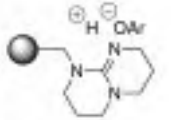
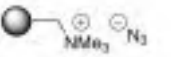
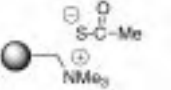
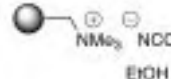
electron-deficient alkenes (Scheme 13).^[146] With α -bromo carboxylic acids **10** has been employed for generating C-radicals which react with aliphatic alkenes and vinyl ethers.^[147]


 Scheme 13. C–C coupling reactions promoted by nickel boride BER **10**.

3.5 Nucleophilic Substitution Reactions

Basic ion-exchange resins, which are loaded with various inorganic and organic anions (see Table 1) are ideally suited for promoting substitution reactions with organic halides and sulfonates. Immobilized phenolates and thiophenolates as well as carboxylates exhibit excellent reactivity. It can be argued that these functionalized resins could also be classified as polymers suitable for the “capture–release” technique (Scheme 1; method D), as the anion is immobilized prior to release into solution. However, many immobilized nucleophiles useful for S_N reactions are of an inorganic nature for which the resin “capture–release” terminology would be stretched too far. For the purpose of conceptual homogeneity organic nucleophiles are also included in Table 7.

Table 7. Polymer-bound nucleophiles in S_N reactions.

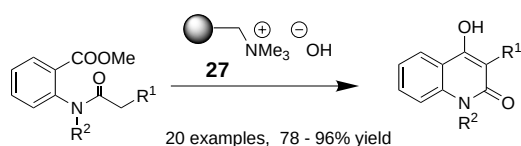
Reagent	Polymeric backbone	Substrate	Product	No. ^[a]	Yield [%]	Ref.
	Amberlite IRA 900 IRA 400 IRA 400	RX, X = Cl, Br, I Me ₂ SO ₄ <i>t</i> BuMe ₂ SiCl	ROAr MeOAr <i>t</i> BuMe ₂ SiOAr	20 11 7	0 – > 99 40 – 92 65 – 96	[148] [149] [150]
	Amberlite IRA 400	MeC(O)CH ₂ Cl		8	89 – 96	[151]
	PS	RX, R = Acyl, Allyl, X = Cl, Br Ar ¹ F	ROAr Ar ¹ OAr	11 2	47 – 98 73 – 75	[152] [152]
	Amberlite IRA 400	RX, X = Cl, Br	ArSR	8	93 – 99	[153]
	Amberlite IRA 400	RX, X = Br	RCN	7	52 – 98	[154]
	Amberlite IRA 400	RX, X = Cl, Br, I, OTs	RN ₃	16	60 – > 99	[155]
	Amberlyst A-26	RX, X = Cl, Br, OTs	CH ₃ COSR	11	80 – 95	[156]
	Amberlyst A-26	RX, X = Cl, Br	RSCN	4	49 – 91	[159]
	Amberlite IRA 400			3	68 – 86	[157]
	Amberlyst A-26	RCH ₂ X, X = Br, I	RCH ₂ OH	7	90 – 95	[158]
	Amberlite IRA 400	RX, X = Cl, Br	RNO ₂	7	10 – > 99	[148]
	Amberlyst A-26	RX, X = Cl, Br		2	83 – 85	[159]
	Amberlyst A-26	RX, X = Cl, Br, I	RSePh	7	76 – > 99	[160]

[a] Number of examples.

3.6 Polymer-Supported Deprotonation

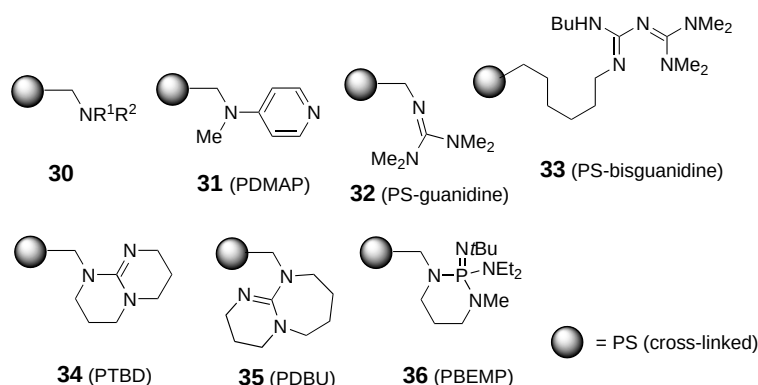
Polymer-bound bases have been widely employed for the deprotonation of organic substrates, alkylation, and acylation reactions. Basic ion-exchange resins such as **27**^[161] can be used for the preparation of 4-hydroxyquinolin-2(1*H*)-ones by an

intramolecular Claisen-type condensation (Scheme 14).^[162] During this reaction polymer-supported carbonate, a rather strong base in organic solvents, and the less-basic immobilized acetate (see Scheme 34) are produced. The reactivity differences of these bases allow for selective transformations.^[163]

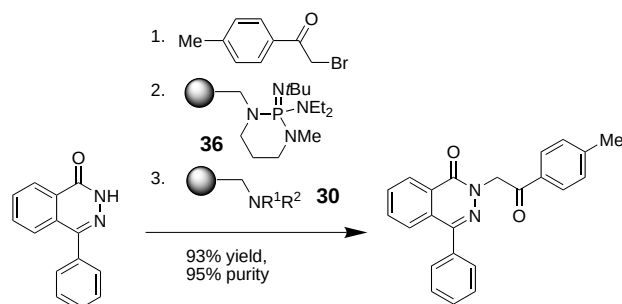


Scheme 14. Intramolecular Claisen-type condensation promoted by basic ion-exchange resin **27**.

In some cases, the polymer-support is directly deprotonated with strong bases like butyllithium or by radical anion induced reductive metallation of polymer-bound thioethers.^[164] These procedures afford metallated polymers which show similar properties to LDA or the lithiated trityl group.^[165] Further important polymer-anchored bases are readily obtained when Merrifield resin is treated with primary and secondary amines. By means of this substitution aminomethylpolystyrenes **30**, polymer-supported dimethylaminopyridine (PDMAP) **31**,^[166] guanidines **32**^[167] and **33**,^[168] and particularly the cyclic analogues, such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene^[169] (PTBD) **34** and 1,8-diazabicyclo[5.4.0]undec-7-ene^[169] (PDBU) **35** have become available. Even Schwesinger's phosphazene base, can be conveniently attached to a polymeric support P-BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphonine) **36**^[170] without loss of the strong basic character ($pK_B = 27.5$ in CH_3CN).

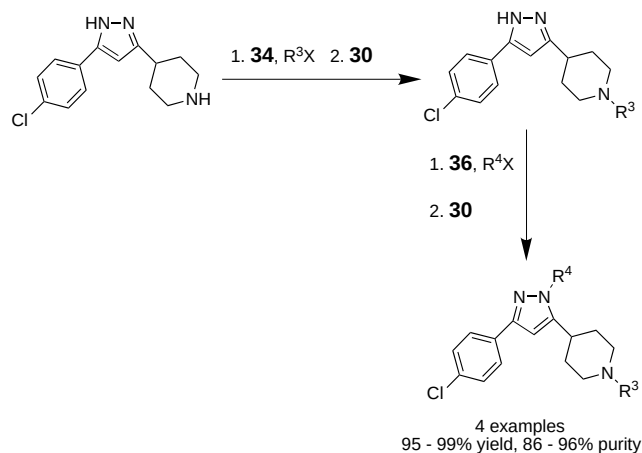


These bases have been utilized for N-benylation of amines^[171] as well as N-alkylation of weakly acidic aromatic N-heterocycles.^[172] Treatment of 2*H*-phthalazin-1-one with α -bromo ketone in the presence of **36** efficiently yields an N-alkylated product with high purity (Scheme 15).^[166] In addition, aminomethylpolystyrene **30** ($R^1 = R^2 = \text{H}$) was added to remove remaining excess of alkylating agent.



Scheme 15. Base-promoted alkylation of 4-phenyl-2*H*-phthalazin-1-one.

In comparison to PBEMP **36**, reagent PTBD **34** shows reduced basicity and has turned out to be an inefficient base for the deprotonation of aromatic N-heterocycles. Nevertheless, polymer-bound base **34** promotes alkylation of piperidines, this property was exploited in a two-step one-pot alkylation cascade leading to alkylated pyrazoles (Scheme 16).^[173]



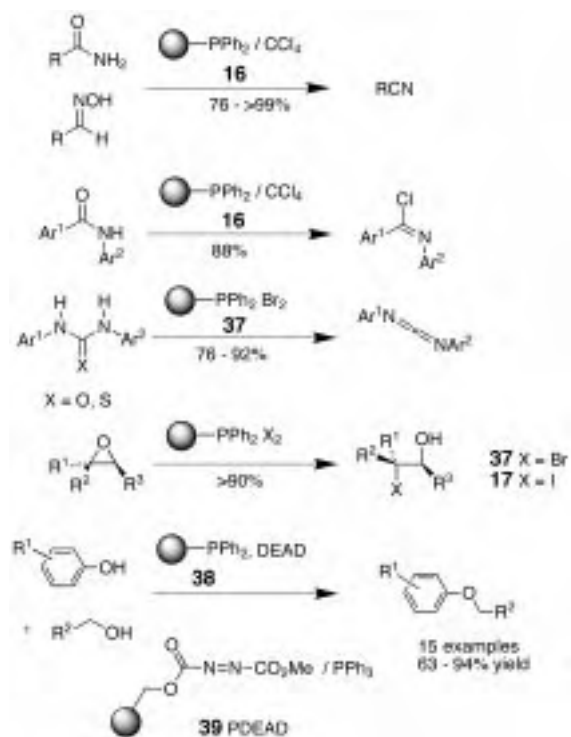
Scheme 16. Polymer-bound bases **30** ($R^1 = R^2 = \text{H}$), **34**, and **36** in a two-step one-pot alkylation of piperidinyl pyrazole.

3.7 Miscellaneous

Various functionalized polymers derived from triphenylphosphane are strongly dehydrating (Scheme 17).^[174] Thus, the reagent system poly-TPP/ CCl_4 **16** can be used to transform primary carboxamides and aryl oximes into nitriles;^[175] imidoyl chlorides are generated when secondary amides are employed instead. Polymer-supported triphenylphosphane dibromide **37** is ideally suited for the preparation of unstable carbodiimides from ureas and thioureas.^[176] Furthermore, poly-TPP-dihalides **17** and **37** promote esterifications of carboxylic acids,^[177] acetalization of carbonyl compounds,^[178a] and can be used for promoting ring opening of oxiranes to the corresponding halohydrins. The mild workup and simple removal of the phosphane from the reaction mixture enables the unstable products to be isolated in high yields.^[178b]

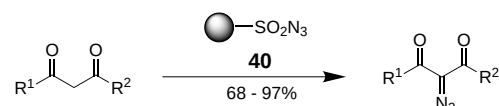
Another important use of polymer-bound triphenylphosphane **38** is the Mitsunobu-reaction, for example, by coupling phenols and alcohols to aryl ethers in the presence of diethyl azodicarboxylate (DEAD).^[179] Alternatively, the polymer-assisted Mitsunobu reaction was achieved by immobilizing alkyl azodicarboxylates on polystyrene.^[180] Reagents like **39** are able to replace hydroxy groups by oxygen, nitrogen, and carbon nucleophiles with an efficiency comparable to that of the solution methods. Furthermore, polymer-supported triphenylphosphane **38** promotes the isomerization of (*Z*)-nitro olefins to the corresponding (*E*)-isomers in high yield and with excellent selectivity.^[181]

Polymer-bound tosyl azide **40** was prepared from Amberlite XE 305 by chlorination with chlorosulfonic acid followed by



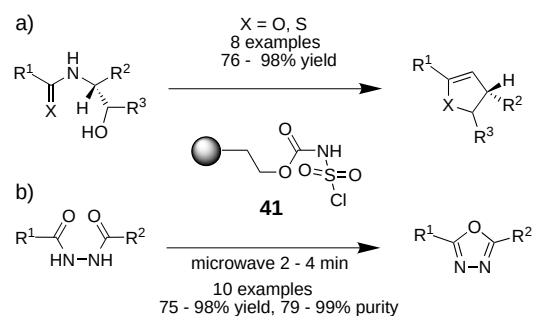
Scheme 17. Polymer-bound triphenylphosphane.

displacement of the chlorine in the intermediate polymer-supported sulfonyl chloride with azide. Reagent **40** is able to promote diazo transfer onto β -dicarbonyl compounds (Scheme 18).^[182]



Scheme 18. Polymer-supported sulfonyl azide.

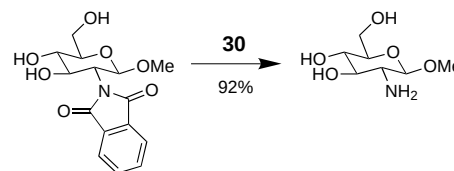
The first example of a soluble polymer-supported Burgess reagent was disclosed by Wipf and Venkatraman.^[183] They employed **41** (attached to PEG) for the cyclodehydration of β -hydroxy amides and thioamides to oxazolines and thiazolines, respectively (Scheme 19). The utility of these reagents was further demonstrated in the synthesis of 1,3,4-oxadiazoles



Scheme 19. Applications of polymer-bound Burgess reagent; a) PEG polymer, b) cross-linked PS.

starting from 1,2-diacylhydrazines with microwave radiation (**41** attached to Merrifield resin).^[184]

The N-phthalimido and N-tetrachlorophthalimido groups on carbohydrate derivatives are removed using alkyl diamines immobilized on polystyrene, thereby leaving the protecting group on the resin while the free sugar remains in solution (Scheme 20).^[185]

Scheme 20. Polymer-supported deprotection of the carbohydrate-bound phthalimido group ($R^1 = H$, $R^2 = CH_2NH_2$).

Finally, acylation including trifluoroacetylation^[186] of amines, carboxylic acids,^[187] and alcohols,^[188] as well as the formation of internucleotide bonds^[189] has been achieved with various polymer-bound reagents and some selected examples of these reagents are given in Section 5.

4. Polymer-Assisted Purification

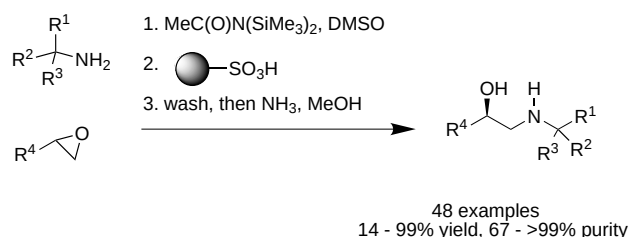
In automated parallel solution-phase chemistry each aqueous extractive workup requires the optimization of a new step and usually a need for chromatographic purification. Polymer-assisted purification techniques offer the chance to circumvent these extraction and chromatographic purification steps. Usually the removal of an excess of a reagent, unreacted starting materials, or by-products from reaction mixtures is achieved by employing polymer-supported reagents with complementary reactivities.^[190] Three closely related variants of polymer-assisted purification protocols have been reported: 1) solid-supported scavengers, 2) sequestration by “tagging” the impurity with the help of sequestration enabling reagents (SER) prior to its polymer-assisted removal, and 3) sequestration by post polymerization. Each method will be briefly discussed.

4.1 Scavenging Reagents

In 1999 several review articles about polymer-supported scavenger reagents (Scheme 1, method C), the most widely utilized functionalized polymers for purification, were published^[10, 190, 191] so that only selected examples are given in this report. These reagents can be roughly divided into scavengers for electrophiles and for nucleophiles. It is clear that the principle behind the standard scavenging protocols is the same: electrophiles react with polymer-bound nucleophiles and acids can be removed with polymer-bound bases and vice versa. This complementary reactivity has been used in nearly all carbon–heteroatom bond-forming reactions. Despite the wealth of methods for the removal of these functionalized compounds, there are few—if any—examples of the scaveng-

ing of reactants from C–C coupling reactions. This may be because of the lack of need as protocols for organometallic complexes in automated solution-phase parallel synthesis are rare.

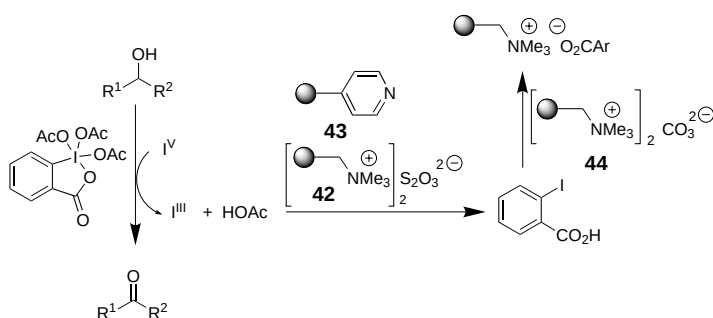
Often ion-exchange resins have served as functionalized polymers for purification. They can either serve as acidic or basic catalysts in parallel solution chemistry or as scavenger reagents for by-products or reaction products. An advantage of ion-exchange resins is that they can be simply reactivated after the sequestration step. This property was exploited in the purification of molecules that can be protonated by ion-exchange chromatography with acidic resins, and has occasionally been combined with acid or base catalysis in preceding reactions.^[148a, 192] An example of this method is the deprotection of *tert*-butoxycarbonyl (Boc) protected amines mediated by Amberlyst A-15 and their purification by ionic resin capture.^[193] To enhance the use of ion-exchange resins they have been loaded with other counter ions which not only allow purification by neutralization but also by, for example, oxidation or reduction (for examples see Table 7). Even incompatible functionalities can be employed using mixed-bed reactors (Scheme 21). Excess Dess–Martin periodinane as well as its reduced iodine(III) form were removed



Scheme 22. Polymer-supported purification after aminolysis of oxiranes.

A large number of covalently bound reagents for scavenging certain functional groups are known of which only the most important examples are summarized in Table 8. One of the earliest examples of the purification of reaction mixtures by using polymeric scavengers was described by Fréchet and co-workers. in the early eighties.^[196] They developed a methodology for removing allergenic α -methylene- γ -butyrolactones from natural oils by using aminated polystyrene resins (Table 8, entry 5). In their detailed study the influence of cross-linking, the chain length of the aminoalkyl residue, as well as the nature of the solvent on the efficiency of the scavenging process was addressed. Recently, Coppola^[197a] along with Fréchet^[197b] and co-workers disclosed a new scavenger reagent for amines (Table 8, entry 6). Thus, it is possible to attach isatoic anhydride to a Merrifield resin which then readily reacts with amines to form CO₂ as the only by-product.

Aldehydes and ketones are removed under mild conditions using polymer-supported *p*-toluenesulfonyl hydrazide (PS-Ts-NHNH₂; Table 8, entry 1).^[198] In comparison with polymer-bound benzyl hydrazide the PS-Ts-NHNH₂ is better suited for storage and it shows superior scavenging properties. In thorough studies, it was shown by Dressman, Hahn, and co-workers^[202] and by Booth and Hodges^[204] that polymer-bound amines are efficient scavenger reagents for isocyanates, acid chlorides, and many other electrophilic functional groups after these substrates have been employed in solution-phase parallel synthesis (entry 2). Polystyrene-based benzaldehyde was used for removing various nucleophiles including amines, hydrazines, keto esters, reducing agents, C-nucleophiles such as Meldrum's acid, and organometallic reagents (entry 7).^[199–202, 209] In this context, it is noteworthy that polymer-bound isocyanate, which behaves in a similar manner to formyl polystyrene, has been employed for distinguishing between secondary and tertiary amines.^[204] For scavenging α -halogenated carbonyl compounds from complex reaction mixtures polymer-bound thiourea has served as a suitable reagent (entry 4).^[208] Another scavenging reagent, namely polymer-supported guanidine, has been developed for removing remaining triscarboxyethyl phosphane, phosphane oxide, as well as HBr (entry 10).^[210] Recently, *N,N*-diethanolamino-methyl polystyrene was prepared to accomplish purification of Suzuki cross-coupling products (Table 8, entry 12).^[213] Nucleophilic addition of alkyl anions to carbonyl compounds affords intermediate alkoxides which are protonated by ion-exchange resin **45**. In addition, unreacted or excess aldehyde is sequestered as an imine by the polymeric amine **30** ($R^2 = H$, $R^3 = (CH_2)_2NH_2$; Scheme 23).^[201]



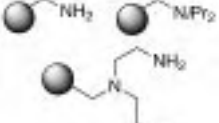
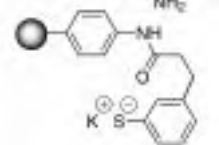
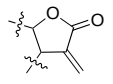
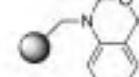
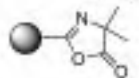
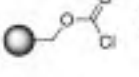
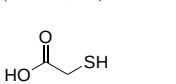
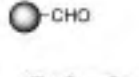
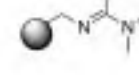
Ref. [194a] 8 examples; 68 - 97% yield
Ref. [194b] 28 examples; 9 - 94% yield, 68 - >99% LC-purity

Scheme 21. Polymer-supported purification of by-products formed in the Dess–Martin oxidation.

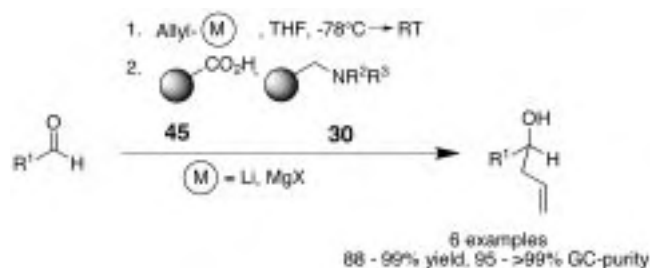
by Amberlyst A-26, loaded with thiosulfate **42**, to form *o*-iodobenzoic acid. In addition, acetic acid which was formed as a by-product was scavenged by poly(4-vinylpyridine) **43**. Finally, the third functionalized polymer, Amberlyst A-26 in the carbonate form **44**, or other polymer-supported bases such as **30** ($R^1 = R^2 = Me$) and **34** were used to remove the *o*-iodobenzoic acid from the reaction mixture. Remarkably, sequential purification was unnecessary.^[194]

Ethanolamines were prepared by a highly optimized three component reaction using primary amines which were *N*-silylated in situ followed by nucleophilic addition to various oxiranes (Scheme 22).^[195] Using this procedure, bisalkylation of the primary amines was avoided. Finally, the use of a cation-exchange resin allowed rapid purification of a library containing 48 compounds.

Table 8. Covalently immobilized scavenging reagents.

Entry	Functional group to be scavenged	Reagent ^[a]	Ref.
1	RCHO, RCOR'		[198]
2	RCO ₂ H, RSO ₃ H, RCOCl, RSO ₂ Cl, RNCO, RNCS, (RCO) ₂ O, RCHO		[199–206]
3	RX		[207]
4			[208]
5			[196]
6	RNH ₂		[197]
7	R ¹ R ² NH		[199–202, 209]
8	RLi, RMgX (X = Br, Cl)		[201]
9			[205]
10			[210]
11	reductive work-up of ozonolysis reaction		[211]
12	R ₂ B(OH) ₂		[212, 213]
13 ^[b]	RCO ₂ H		[214]

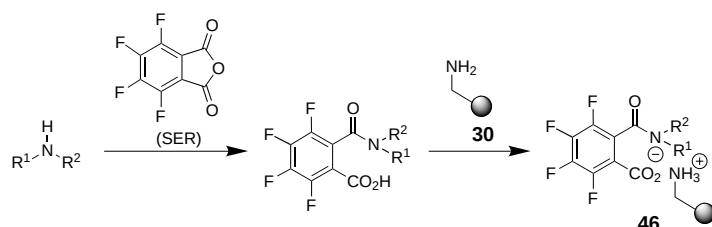
[a] Polystyrene (1–2% cross-linked with DVB). [b] Wang-resin.



Scheme 23. Polymer-supported scavenging of by-products generated in the nucleophilic alkylation of aldehydes.

4.2 Purification by Using “Tagging” Reagents

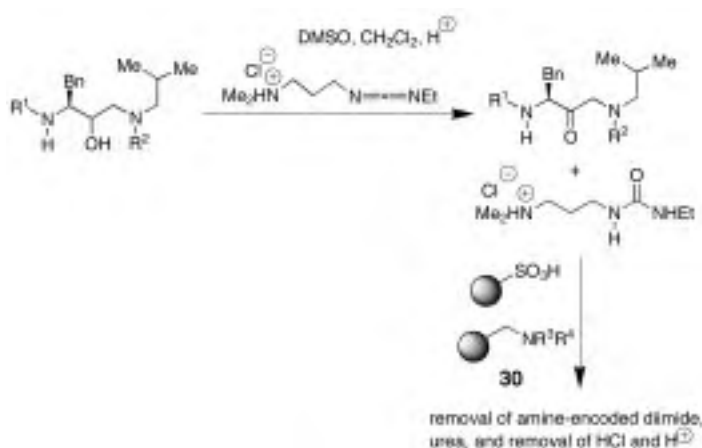
Sometimes by-products are not reactive enough to be scavenged quantitatively by functionalized polymers. For this reason, highly active bifunctional soluble compounds, termed “sequestration enabling reagents” (SERs), were developed. These reagents transform less-reactive functional groups, in solution, into easily scavenged species. Examples exist for both electrophilic and nucleophilic SERs.^[215] The “tagging” of reactive functional groups is most often accomplished with amino groups. They play the active role in the sequestration process by reacting with the polymer-based scavenger reagents listed in Table 8, entry 7. Treatment of an excess of amine with the highly electrophilic tetrafluorophthalic anhydride leads to an addition product which then can be sequestered as polymer **46** with the help of the polymer-bound amine **30** (Scheme 24).^[200, 216]



Scheme 24. Tetrafluorophthalic anhydride, a sequestration enabling reagent for amines.

The concept of scavenging enabling reagents is closely related to that of a second method, that is the tagging of soluble reagents or products. An example of a soluble, “tagged” reagent is presented in Scheme 25. Parlow and co-workers developed an elegant purification strategy for the Pfitzner–Moffat oxidation of alcohols to the corresponding carbonyl compounds.^[201] The parallel oxidation of hydroxyethyl amines was effected by a tertiary-amine-tagged carbodiimide in combination with DMSO and a catalytic amount of acid. The tagged urea and carbodiimide resulting from this process as well as acids were then scavenged by employing two ion-exchange resins.

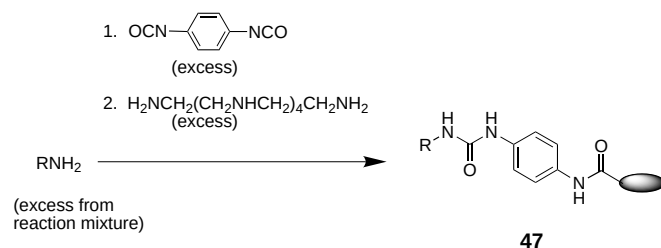
Only in a few cases has the product been tagged. Crown-ether-tagged peptides were readily separated from the reaction mixture by affinity chromatography using amino-methylated (in CF₃CO₂H form) polystyrene columns.^[217]



Scheme 25. “Tagged” carbodiimide in Pfitzner–Moffat oxidations and purification by ion-exchange resins ($R^3 = R^4 = \text{methyl}$).

4.3 Purification by Post Polymerization

Barrett, Smith, and Zecri added the latest method to the growing number of purification techniques based on insoluble materials which they named “impurity annihilation” (Scheme 26).^[218] This method, in fact, does not rely on



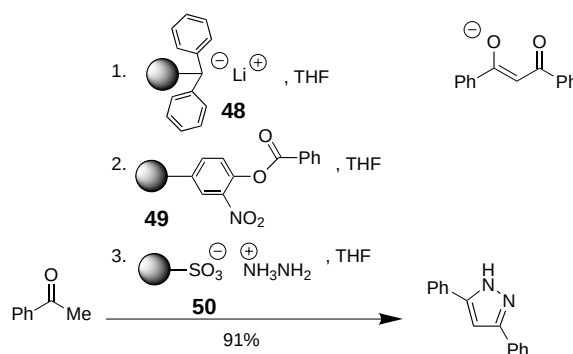
Scheme 26. Removal of amines by incorporation into a polyurethane matrix.

polymer-bound reagents. Instead, a soluble polyamine is added to the reaction mixture and the insoluble polymer support is formed during the process of scavenging. Thus, after performing amide or sulfonamide bond-forming reactions excess amines were treated with excess 1,4-phenylene diisocyanate and then with pentaerythritol hexamine affording the insoluble polyurea **47** which can easily be removed by filtration. This strategy requires very careful optimization of the reaction conditions to avoid the creation of soluble impurities by the reaction of the diisocyanate with two equivalents of the amine to be scavenged. Furthermore, yields for the product could be reduced by trapping during the polymerization process. However, “impurity annihilation” shows promise because only solutions are employed, which allows automation through liquid-handling robots.

Despite the fact that only selected examples have been listed here, it is evident that, with the sheer number of possibilities of functionalizing polymers as well as tagging soluble reagents, purification based on scavenging techniques will play an increasing role in automated solution-phase synthesis in the future.

5 Polymer-Assisted Multistep Solution-Phase Syntheses

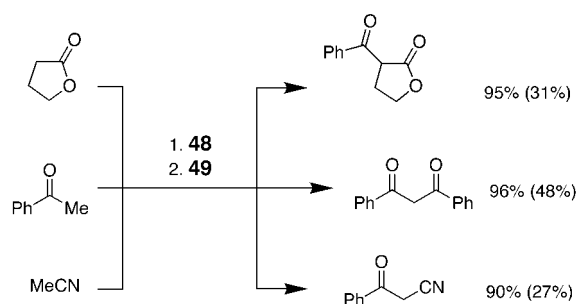
The renewed interest in functionalized polymers whether employed stoichiometrically or as catalysts will only prevail and be sustained if they prove to be powerful tools in automated parallel synthesis and multistep sequences. For this purpose, all the synthetic techniques that were presented in Sections 3 and 4 and in addition the emerging polymer-supported catalysts need to be combined in an intelligent and creative way. Much evidence has already been collected, particularly by applying scavenger reagents and in employing “capture–release” technology, which shows that functionalized polymers can be employed conveniently in automated parallel synthesis by using conventional automation facilities such as liquid-handling devices. As shown in Scheme 32 compound libraries with up to 88 members were generated using this solid-phase technique. However, up to now multistep syntheses promoted by functionalized polymers have led to hardly any novel synthetic sequences. As long as the number of polymeric reagents is limited, this field can only follow known strategies by successively exchanging soluble reagents by their parent polymer-anchored counterparts. In this context, the Patchornik group^[219] was the pioneer in this field. Unlike contemporary strategies, they initiated their studies by anchoring two different reactive groups, namely an enolizable and a nonenolizable ester to the same resin and studied the base-promoted “intrapolymeric” condensation, which proceeded in much better yields and with higher purity than the corresponding solution variant. As a continuation of their work, Cohen, Patchornik, and Kraus switched their attention to the development of the first multicomponent synthesis based on several reagents attached to different polymer supports, which they named “Wolf and Lamb” reactions (after Isaiah 11:6 in the Old Testament).^[220] In the presence of acetophenone they employed two insoluble polymer-supported reagents **48** and **49** which are “antagonists” in solution. Immobilized, and thus spatially separated the functionalized polymers did not interact when mixed (Scheme 27). Polymer-attached triphenylmethyl lithium **48** promoted deprotonation while reagent **49** acted as an acylating agent.^[221] The acylation product, the dibenzoylmethane anion, was directly treated with polymer-supported hydrazine **50** to afford a disubstituted pyrazole in excellent yield. In a



Scheme 27. The first three-step synthesis aided by polymer-bound reagents.

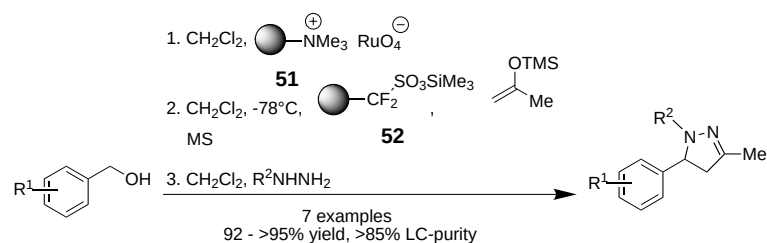
control experiment in solution the ketone formed in the first step was generated in reduced yield (48 %), because it is more acidic than the starting ketone and thus protonates the starting enolate. The important message from this work was, that two reagents possessing high reactivity toward each other are rendered completely inactive by their attachment to two insoluble polymers. In such reactions both kinetic factors and equilibrium conditions differ from those prevailing in conventional reactions in solution, or in reactions utilizing a single polymeric reagent.^[222]

In a later more detailed study, the use of strong bases such as **48** or polymer-supported LDA in conjunction with an acylating agent such as **49** was verified, using various CH-acidic organic substrates (Scheme 28).^[165] A comparison of isolated yields for the final products was conducted and clearly revealed the superiority of the polymer-supported process over the pure solution variant.



Scheme 28. Polymer-supported α -acylation of CH-acidic compounds. The yields in parentheses are from the reaction in solution.

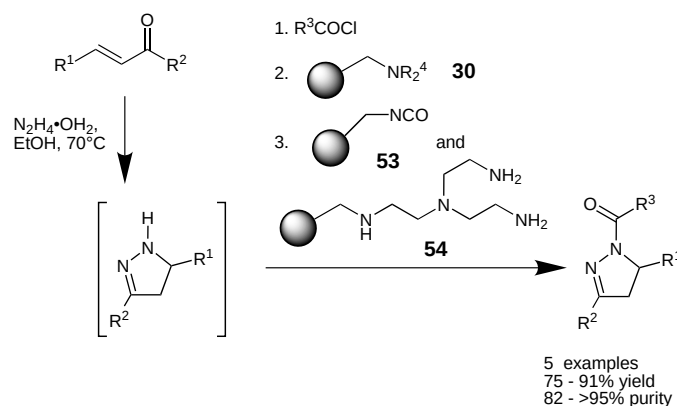
For the preparation of a library composed of 4,5-dihydro-1*H*-pyrazoles two polymer-supported reagents **51** and **52** were successfully employed (Scheme 29).^[223] The sequence was initiated by oxidation of six different benzyl alcohols to the



Scheme 29. Polymer-supported synthesis of 4,5-dihydro-1*H*-pyrazoles (version 1). MS = Molecular sieve (4 Å).

corresponding benzaldehydes. Then a Mukaiyama aldol reaction was conducted by coupling these aldehydes with silyl enol ethers. This step was mediated by polymer-supported TMSOTf (TMS = trimethylsilyl; Nafion-TMS) **52** in the presence of 4 Å molecular sieves as a dehydrating agent, a reaction which is noteworthy, as it demonstrates that functionalized polymers may also be employed at low temperature. The synthesis was finally accomplished by treatment of the intermediate α,β -unsaturated ketones with hydrazine or methyl hydrazine to afford the target heterocycles in high yields after removal of volatile compounds.

An alternate polymer-assisted synthesis of pyrazoles was disclosed recently^[224] in which the treatment of chalcones with hydrazine monohydrate resulted in unstable pyrazoline intermediates (Scheme 30). These intermediates were trapped in the presence of polymer-bound base **30** with electrophiles such as acid chlorides to provide N-acylated pyrazolines. A scavenging cocktail of polymer-supported isocyanate **53** and trisamine **54** was used to remove remaining pyrazoline and excess electrophile, respectively.

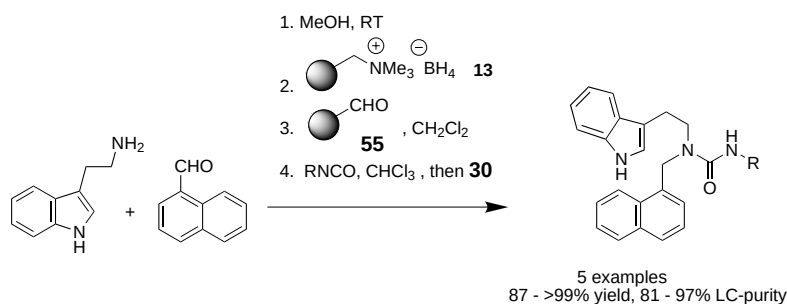
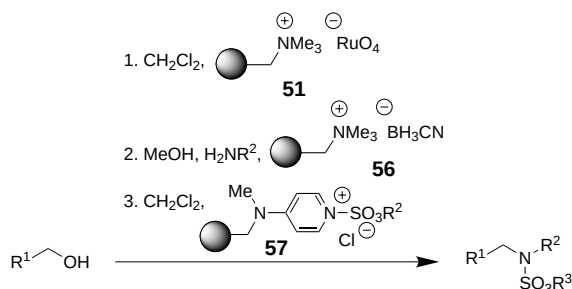


Scheme 30. Polymer-supported synthesis of pyrazoles (version 2; $R^2 = R^3 = 2$ -propyl).

Trisubstituted ureas were prepared from three building blocks (Scheme 31).^[199] Aldehydes and amines were coupled by means of reductive amination^[225] with polymer-bound borohydride **13**. Excess of the starting amines was removed by polystyrene carboxaldehyde **55**. After filtration addition of a set of isocyanates gave a small library of ureas. Finally, the polymer-anchored amine **30** ($R^1 = R^2 = H$) removed excess of isocyanates.

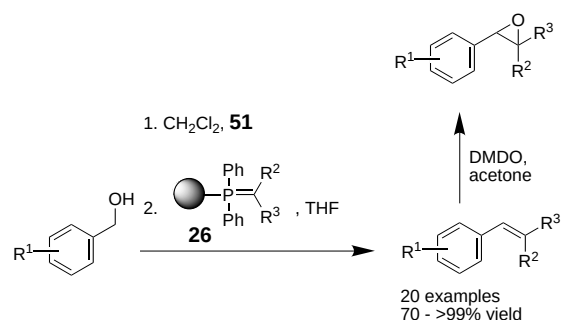
Libraries of amines and sulfonamides were prepared by a three-step process fully controlled by polymer-supported reagents (Scheme 32).^[226] A set of benzyl alcohols was oxidized to the corresponding aldehydes followed by reductive amination in the usual way using reagents **51** and **56** (see also Schemes 29 and 31). The authors point out that solution-phase synthesis using functionalized polymers can be conducted with the technical equipment used in combinatorial synthesis. The primary oxidation products were dispensed into 96 wells each containing the polymer-supported reducing agent. A robot was used to add various amines in methanol to the wells. Finally, the secondary amines were further functionalized using sulfonated amino pyridine polymers **57** which promoted sulfonation to sulfonamides. By using this technique, the preparation of a medium-sized compound library was achieved.

Another access to compound libraries based on polymer-supported reagents utilized polymer-bound phosphorous ylides **26** which were coupled with aldehydes, themselves prepared in the usual manner, to afford di- and trisubstituted alkenes (Scheme 33).^[227] The *Z/E*-selectivity was moderate with the best ratios being 6:1. Finally, additional structural

Scheme 31. Polymer-supported synthesis of trisubstituted ureas $R^1 = R^2 = H$).

intermediate amines: 88 examples, 35 - 92% LC purity, no comments on yields
sulfonamides: 7 examples, >82% yield, > 90% LC purity.

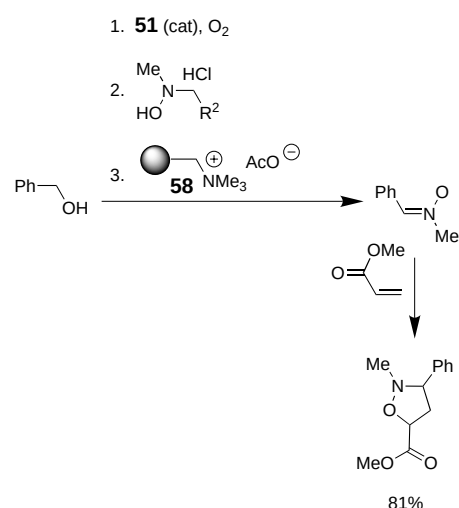
Scheme 32. Polymer-supported preparation of sulfonamides.

Scheme 33. Polymer-supported phosphorous ylides **26** in multistep syntheses (DMDO = dimethyldioxirane).

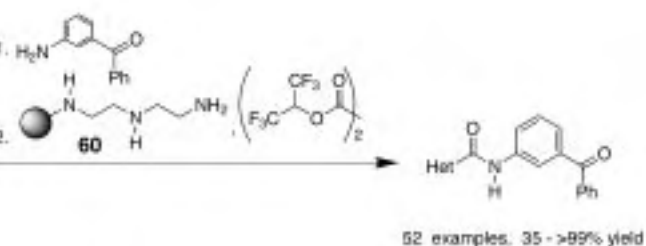
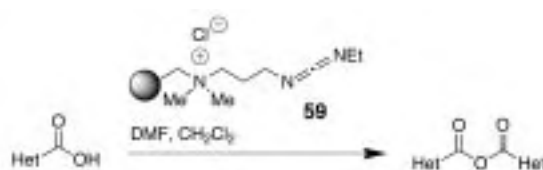
variation was achieved by dimethyldioxirane-promoted epoxidation, a suitable tool in this context, as reagent-derived by-products are commonly removed in vacuo.

Aldehydes prepared from the corresponding alcohols (c.f. Table 1, entry 10 and 11) were transformed into nitrones by condensation with primary hydroxylamines which were initially prepared in situ with the help of polymer-supported acetate **58** (Scheme 34).^[228] Cycloaddition in the presence of methyl acrylate led to isoxazolidines like *N*-methyl-5-methoxycarbonyl-3-phenylisoxazolidine which was generated in a one-pot reaction in 81% yield.

Another multistep synthesis takes advantage of the dehydrating power of polymer-bound carbodiimide **59** in the primary step which was used to prepare anhydrides from the respective heterocyclic substituted carboxylic acids (Scheme 35).^[214c] These anhydrides were treated with a substituted aniline to afford a set of carboxamides. A well orchestrated mixture of additives was employed for removing both the acidic as well as the basic unreacted starting materials.



Scheme 34. Polymer-supported synthesis of isoxazolidines.

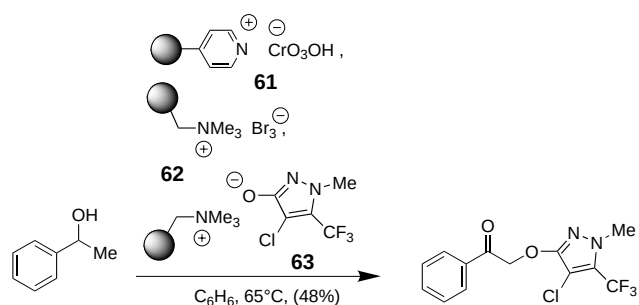


Scheme 35. Preparation of carboxamides involving the SER technique (Het = heterocyclic residue).

Anhydrides and traces of the carboxylic acids were sequestered using polymer-supported amine **60**. In addition, hexafluoroisopropyl oxalate was used as a supporting sequestering reagent (see Section 4.2) to convert unreacted aniline into the monoamide. Both, the oxalate as well as the monoamide were then removed by **60**.

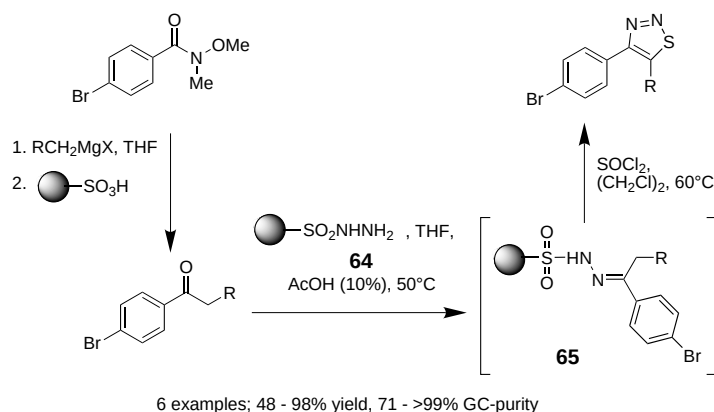
Parlow devised a three-step procedure based on polymer-supported dichromate **61**, perbromide on Amberlyst A-26 **62**, and Amberlite IRA-900 loaded with 4-chloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-ol (**63**) to prepare substituted phenylethanone (Scheme 36).^[229] Although only one compound was prepared the study clearly supports the view that different polymer-supported reagents can be handled simultaneously in one vessel under conditions that allow the soluble substrate to access all three polymers. In fact, when the reagents were employed successively, the substituted phenylethanone was prepared in only 42% (instead of 48%) yield underlying in this case the advantage of a one-pot multistep strategy.

1,2,3-Thiadiazoles were prepared, starting from a Weinreb amide which was alkylated with a variety of Grignard reagents to the corresponding ketones, using a sulfonic acid on a



Scheme 36. Polymer-supported synthesis of substituted phenylethanone.

macroporous support. This led to decomposition of the tetrahedral intermediate (Scheme 37).^[230] α -Methylene ketones are ideal starting materials for the Hurd–Mori cycliza-

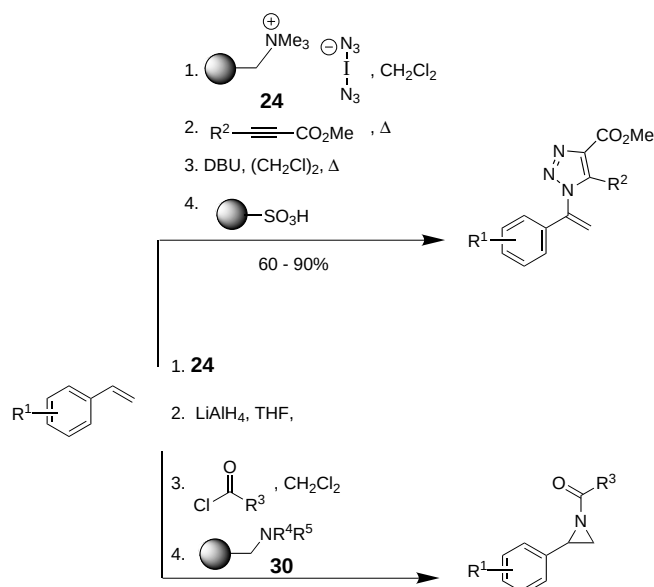


6 examples; 48–98% yield, 71–>99% GC-purity

Scheme 37. Polymer-supported synthesis of 1,2,3-thiadiazoles.

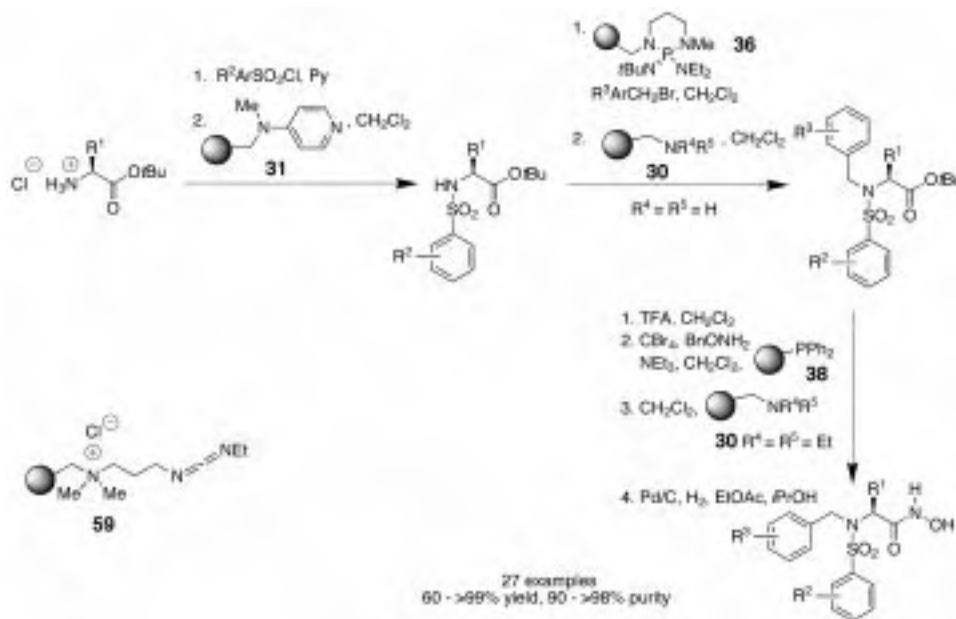
tion.^[231] For this purpose, a gel-type polystyrene-sulfonyl hydrazide resin **64** was employed. Here, the polymeric reagent, which was originally designed for carbonyl scavenging applications (Section 4), was used in a resin capture–release strategy. After the keto group in **65** was trapped by **64** thionyl chloride mediated cleavage led to thiadiazoles in high yield and with good purity.

Azidoiodination of alkenes using novel polymer-based haloate(i) complex **24** provides a very useful entry to various nitrogen-containing heterocycles (Scheme 38).^[130, 232] Thus, the primary addition products were used as 1,3-dipoles in a cycloaddition reaction with electron-deficient alkynes. After removal of excess alkyne in vacuo iodine was removed by elimination affording triazoles. The elimination was initiated with DBU which was finally removed by an acidic scavenging resin. Al-

Scheme 38. Polymer-supported synthesis of triazoles and acyl aziridines (DBU = 1,8-Diazabicyclo[5.4.0]undec-7-en, R⁴ = H, R⁵ = CH₂CH₂NH₂).

ternatively, α -iodo azides were transformed into the unprotected aziridines which are ideally suited for acylation. In this case, excess acylating agent was scavenged by the basic polymer **30** (R⁴ = H, R⁵ = (CH₂CH₂NH₂)₂).

Hydroxamic acids are known to exert an inhibitory effect on the matrix metalloproteins (MMP) class of enzymes. Polymer-supported reagents proved to be a very useful tool for constructing a small library of chiral hydroxamic acids (Scheme 39).^[233] The *tert*-butyl ester hydrochlorides of glycine, valine, and phenylalanine were converted into aryl sulfonamides under classical conditions followed by using first aminomethyl polystyrene and then Amberlyst A-21 to desalt the solution by binding hydrogen chloride. Alternatively, this



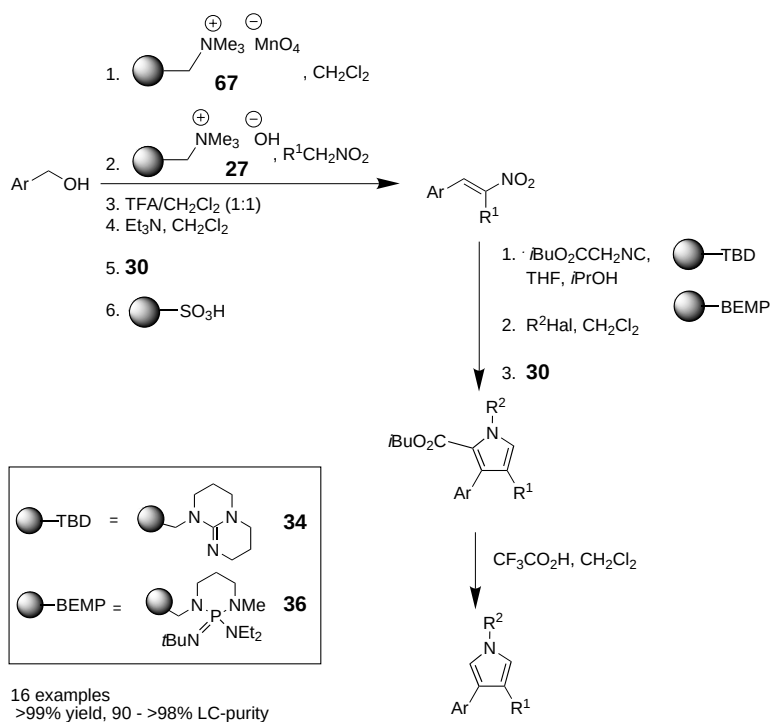
Scheme 39. Polymer-supported multistep synthesis of a hydroxamic acid library.

step can be achieved by activation of the amino group with polymer-supported dimethylaminopyridine **31**. Subsequently, benzylation of the nitrogen functionality was achieved using three equivalents of benzyl bromide and polymer-supported phosphazene base **36**. Excess of the alkylating agent was sequestered with aminomethyl polystyrene. Cleavage of the *tert*-butyl group and activation of the intermediate carboxylic acid in the presence of carbon tetrabromide and polymer-bound triphenylphosphane **38** afforded intermediate acyl bromides which were coupled with *O*-benzyl hydroxylamine to give the corresponding hydroxamic acid esters. For workup, aminomethyl polystyrene **30** was employed for sequestering acid anhydrides, the free acid, and remaining acyl bromides. The sequence was terminated by catalytic hydrogenation to furnish the target compounds. Remarkably, direct formation of hydroxamic acids from the carboxylic acids with *O*-benzyl hydroxylamine using polymer-supported cyclohexyl carbodiimide **59** was not successful.

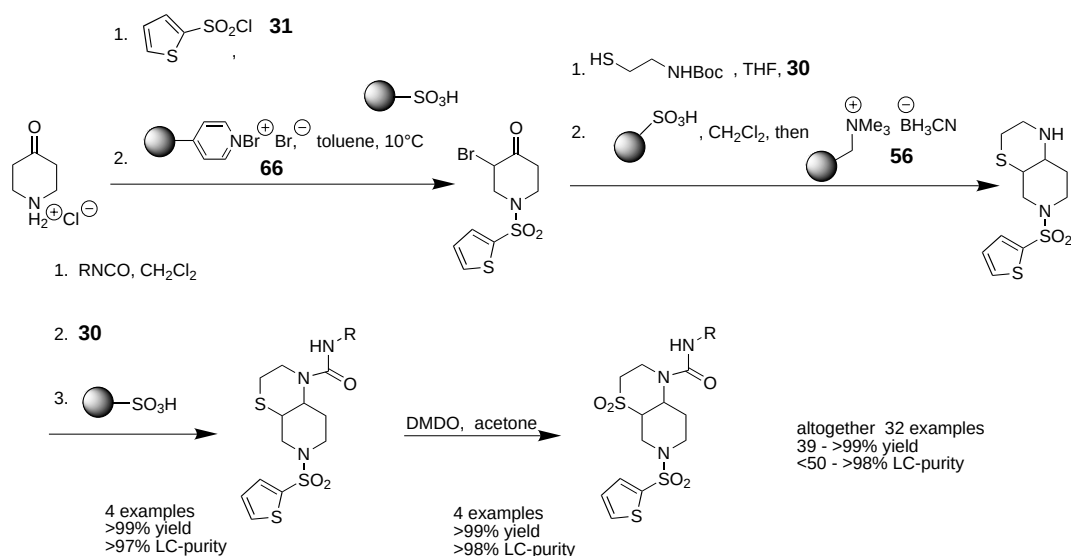
Ley and co-workers developed a route to piperidino-thiomorpholines using a series of polymer-anchored reagents (Scheme 40).^[234] The secondary amino functionality of 4-piperidino hydrochloride hydrate was transformed into various sulfonamides, promoted by polymer-supported (dimethylamino)pyridine **31** followed by the addition of acidic Amberlyst 15 as the sequestering agent. This step was followed by α -bromination of the keto functionality for which polymer-supported pyridinium bromide perbromide **66** was used. The α -bromoketone was then treated with *N*-Boc protected 1-amino-ethane-2-thiol aided by Amberlyst A-21 **30** ($R^1 = R^2 = \text{Me}$) as a base. This treatment effected substitution. After ion-exchange-mediated removal of the protection and imine formation polymer-supported reduction using cyanoborohydride **56** afforded thiomorpholine derivatives (*trans*:*cis* = 2:1). The amino function

was further modified with different isocyanates, by-products, or excess reagent and was sequestered using two polymer-supported reagents. The resulting thiomorpholine derivatives were finally oxidized to the corresponding sulfones using dimethyldioxirane under standard conditions.

Also pyrroles can be prepared by a polymer-supported synthetic sequence (Scheme 41).^[235] Here, the synthesis was initiated by the oxidation of a benzyl alcohol using polymer-supported permanganate **67**. This step was followed by the Henry reaction in which nitroalkanes were deprotonated with Amberlite IRA-420 **27**.^[161] After trifluormethylacylation of the 1-hydroxy-2-nitro compounds elimination was effected by treatment with triethylamine. Final, desalting of the reaction



Scheme 41. Polymer-supported multistep synthesis of pyrroles ($R^3 = R^4 = \text{H}$).



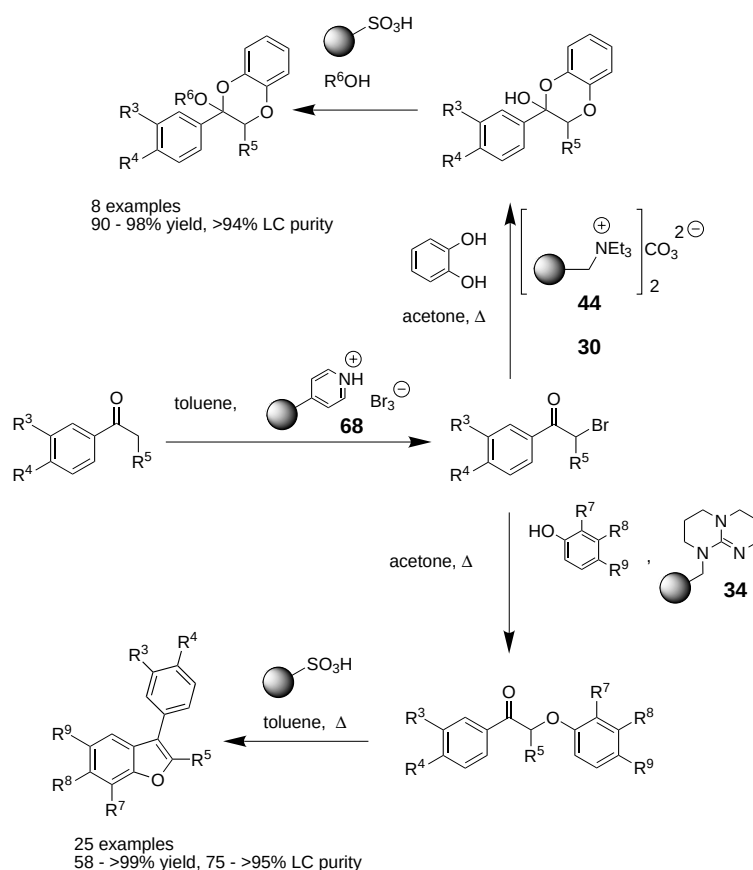
Scheme 40. Polymer-supported multistep synthesis of two piperidino-thiomorpholines.

mixture involved the use of two sequestering agents to afford various nitroalkenes. The pyrrole ring was then constructed by a 1,3-dipolar cycloaddition with *tert*-butyl isocynoacetate in the presence of polymer-supported guanidine base (PTBD) **34**. Alkylation of the ring nitrogen was possible using the very strong polymer-supported Schwesinger's base **36** which yielded tetrasubstituted pyrroles. In conjunction with aminomethyl polystyrene **30** excess alkylating agent was sequestered, followed by decarboxylation by treatment with trifluoroacetic acid to furnish trisubstituted pyrroles.

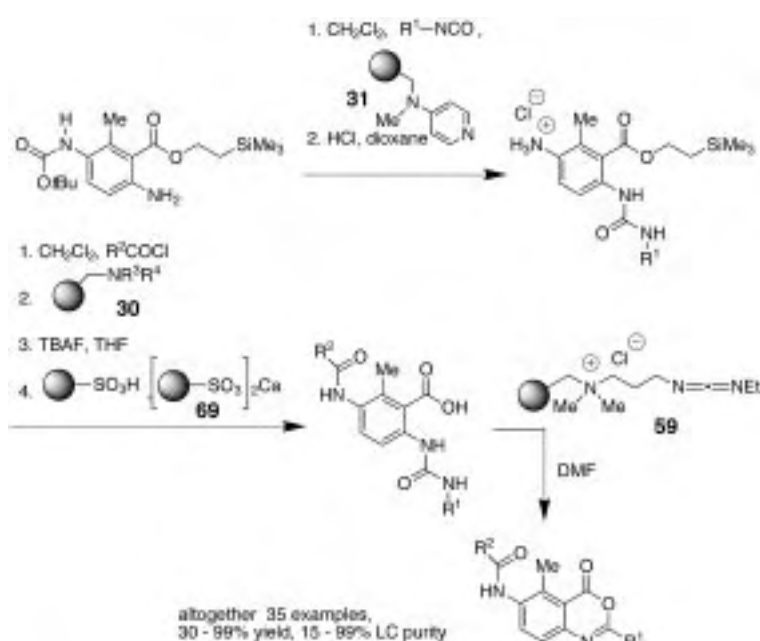
A three-step sequence was developed to synthesize an array of substituted benzodioxane derivatives (Scheme 42).^[236, 237] Substituted acetophenones were initially α -brominated using polymer-attached pyridinium bromide perbromide **68**. Treatment with catechols in the presence of two equivalents of polymer-supported carbonate **44** afforded benzodioxanes as a mixture of the open-chain and ring-closed tautomers. Workup involved the addition of aminomethyl polystyrene **30** which captured unreacted catechol and traces of α -bromo ketones. Finally, a *trans*-acetalization reaction was effected in the presence of the acidic ion-exchange resin Dowex 50 in methanol or ethanol to afford 1,4-benzodioxanes.

In a similar manner, substituted 3-phenyl benzofurans were prepared in three steps from acetophenones by using polymer-supported pyridinium bromide perbromide **68**, triazabicyclodecene **34**, and Amberlyst 15 (Scheme 42). As for most polymer-based multistep syntheses developed no chromatographic purification was required in preparing a library of 25 compounds. When α -brominated acetophenones were treated with a strong polymer-bound base and thiourea 2-amino-1,3-thiazoles (four examples) were formed, again with high yields (47–>95%) and excellent purities (>95%).^[236]

Finally, a five-step solution-phase synthesis of a benzoxazino library based on functionalized polymers accomplished by Parlow, Vazquez, and Flynn is worth mentioning (Scheme 43).^[238] Suitably protected bisfunctionalized aniline served as a starting scaffold to allow for orthogonal deprotection. Acylation of the amino group was supported by polymer-bound dimethyl pyridinamine **31** which allowed the scavenging of excess acylating agents. Proton-induced removal of the Boc-group afforded aniline hydrochloride salts. This paved the way for acylating the second amino group and here again the product was purified with the help of a polymer-supported amine **30** ($R^3 = R^4 = \text{Me}$). Deprotection of the 2-(trimethylsilyl) ether under classical conditions (tetrabutyl ammonium fluoride (TBAF)) was followed by use of two polymer supported reagents which allowed efficient desalting of the reaction mixture. While polymer-bound sulfonic acid helped to remove the tetrabutyl ammonium cation from the



Scheme 42. Synthetic routes to benzodioxanes and benzofurans promoted by polymer-supported reagents (**30**: $R^3 = R^4 = \text{H}$).



Scheme 43. Polymer-supported synthesis of a benzoxazino library ($R^3 = R^4 = \text{Me}$).

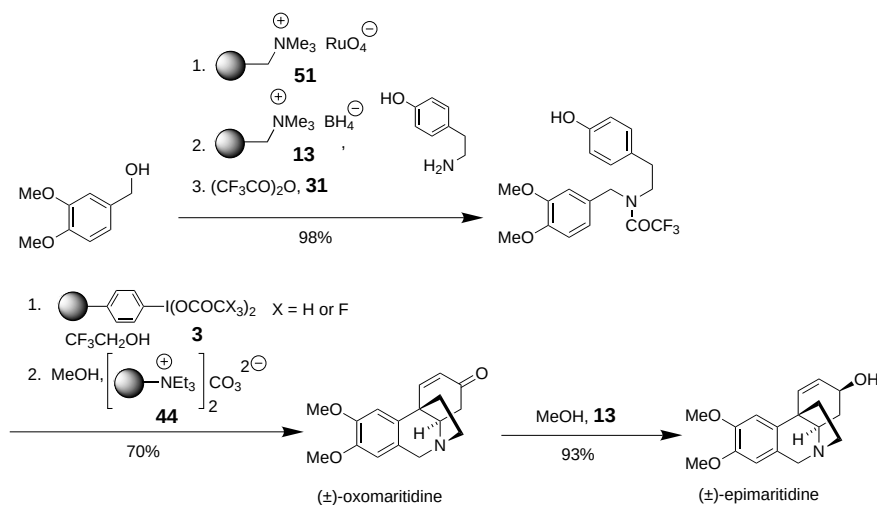
corresponding acid by filtration, the immobilized calcium salt **69** trapped excess fluoride and led to the formation of insoluble calcium fluoride.^[200] The final step involved ring closure using polymer-supported carbodiimide **59** to provide benzoxazinones. It is noteworthy that the five-step sequence

was performed in an automated parallel fashion using a commercial synthesizer.

6. Natural Product Synthesis with Functionalized Polymers

Very recently, Ley and co-workers dramatically accelerated the pace in the field of solution-phase synthesis using functionalized resins. A set of new multistep sequences based on polymer-supported reagents allowed for the total synthesis of various natural products, in particularly alkaloids.

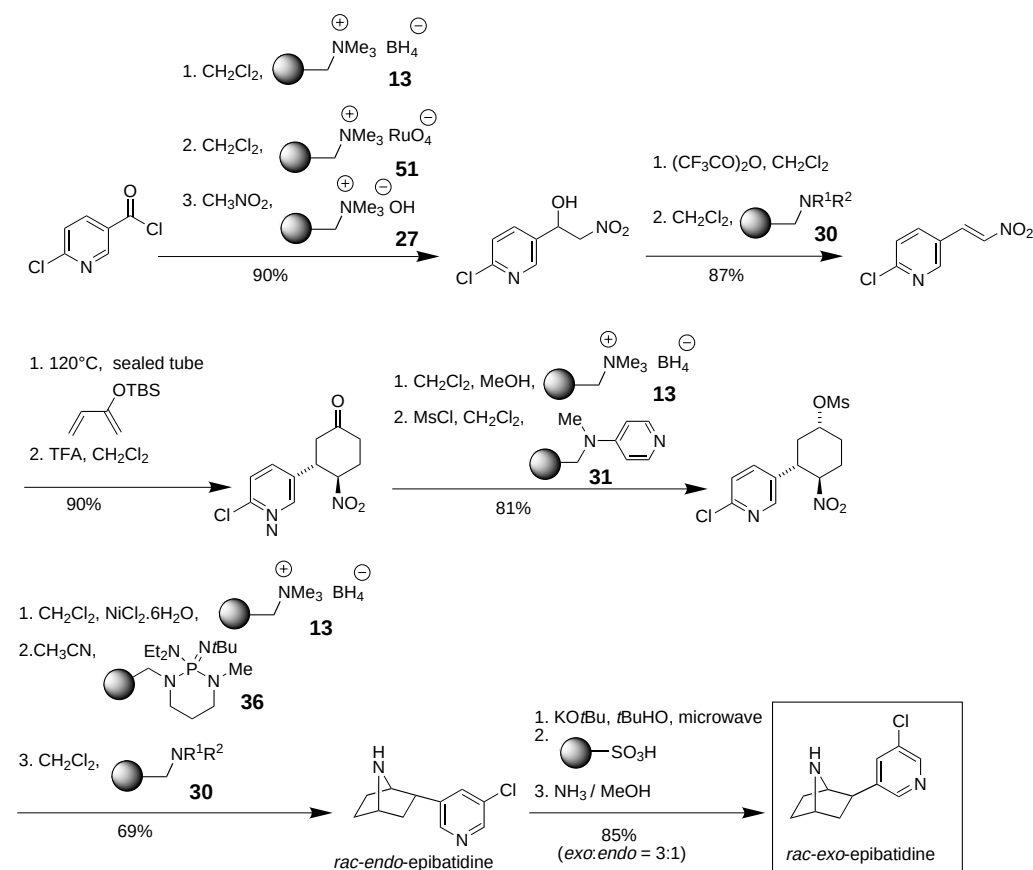
In this context, a concise syntheses of (±)-oxo-maritidine and (±)-epimaritidine were achieved by sequences of five and six consecutive steps, respectively (Scheme 44).^[239] In analogy to a strategy developed by Kita et al.^[240] substituted benzyl alcohol was transformed into trifluoroacetyl amide (90%) in three steps using functionalized polymers **51**, **13**, and **31**. This set the stage for the intramolecular phenolic oxidative cyclization promoted by polymer-supported (diacetoxyiodo)benzene **3** (X = H) or by the trifluoroacetate analogue (X = F). Treatment of the *para*–*para* coupled intermediate product with polymer-supported carbonate **44** resulted in rapid deprotection and spontaneous intramolecular 1,4-addition of the intermediate amine to afford (±)-oxo-maritidine in high yield. The



Scheme 44. Polymer-supported total synthesis of (±)-oxo-maritidine and (±)-epimaritidine.

sequence was terminated by reduction of the keto group by polymer-supported borohydride **13** and provided (±)-epimaritidine.

For the synthesis of the potent analgesic compound (±)-epibatidine, isolated from the Ecuadorian poison frog *Epi-pedobates tricolor*^[241] an even longer synthetic sequence^[242] (12 linear steps; 10 steps mediated by functionalized polymers) based on polymer-supported reagents was designed (Scheme 45).^[243] Starting from an acid chloride, the synthesis was initiated with two polymer-supported functional-group manipulating steps based on functionalized polymers **13** and **51** (reduction to alcohol, oxidation to aldehyde) and one polymer-promoted Henry reaction using nitromethane and base **27** to provide unstable nitro alcohol. Derivatization with trifluoroacetic anhydride, one of the few synthetic steps which is not based on a polymer-supported reagent, followed by treatment with dimethylaminomethyl polystyrene resin **30** ($\text{R}^1 = \text{R}^2 = \text{Me}$) prompted elimination to furnish intermediate *trans* alkene. The thermal Diels–Alder reaction in an undried, sealed vial provided the intermediate silyl enol ether which after removal of excess of diene in vacuo was transformed exclusively into *trans*-



Scheme 45. Polymer-supported synthesis of (±)-epibatidine.

configured cyclohexanone. After this intermezzo without functionalized polymers the sequence was continued by the polymer-supported reduction of the ketone and mesylation using functionalized polymers **13** and **31**. The mesylate formed was further transformed by reduction of the nitro group using nickel-modified BER reagent **13**^[244] followed by transannular cyclization using the polymer-supported version of Schwesinger's base **36** and sequestering of acidic impurities by use of basic aminomethyl polystyrene resin **30** ($R^1 = R^2 = H$). This sequence allowed for the preparation of the *endo* isomer of ($\pm$)-epibatidine (>85% purity by liquid chromatography–mass spectrometry; LC-MS). Final epimerization was achieved by using microwave irradiation. Again, an acidic scavenger resin helped to remove basic components and the products from the reaction mixture. The product was then displaced from the resin with the help of a methanolic solution of NH_3 .

Analogous to the “tea-bag” technology which has been widely used in “split and combine” combinatorial chemistry, pouches filled with the various functionalized polymers were employed in this synthesis. Thus, when a reaction is judged to have gone to completion, the pouch can be removed, washed, and the next reagent-containing pouch can be added to the reaction vessel. The authors note that the syntheses were achieved without chromatographic purification, with excellent yields for most steps, and importantly with minimum optimization.

The last two examples clearly reveal the advantages of stoichiometrically employed functionalized polymers and demonstrate their future prospects.

7. Outlook

Solid-supported reagents have been the subject of research for four decades. The interest shown by the chemical community has varied dramatically, partly because such reagents are relatively costly compared to reagents which are not attached to a polymeric support. Therefore, the ability to recycle stoichiometrically employed solid-supported reagents is a key factor for their wide use in the future. Still, the potential of these polymers was recently demonstrated in optimized solution-phase synthesis and compound-library generation. Therefore, it is reasonable to assume that polymer-supported reagents will be employed with increasing regularity to conduct one- to multistage synthetic sequences. They will routinely find use in automated parallel synthesis, in particular, for creating compound libraries which are difficult to construct on a polymeric support. To facilitate this use, the technique requires rapid development, in particular in the following areas: 1) the search for new functionalized polymers, 2) the development of new solid supports with properties specifically optimized for the synthetic procedure, 3) the development of new multistep sequences, 4) automation with improved “hardware” and subsequently 5) miniaturization as summarized below.

In fact, all the advantages of using polymers in organic synthesis can be exploited fully when the various techniques are mixed, not only those mentioned herein but also immobilized catalysts. These catalytically active polymers, in

particular those based on transition metals, show great promise for future applications. Once some drawbacks, such as stability, recovery, and metal leaching, have been resolved, they will play an important role in multistep syntheses, particular in the key steps involving C–C bond forming processes. Many of these catalytic processes will be coupled with scavenging techniques (Section 4), which by then will be even more sophisticated. Indeed, the coupling of these two processes is essential when the removal of by-products or an excess of one reactant becomes necessary. Soon, hybrid techniques will become available that use both solid-phase organic synthesis followed by derivatization of the functional groups with polymer-supported reagents after the release and cleavage of the substrate from the polymer.^[245] These developments will also enhance the utility of soluble polymers in automated parallel synthesis. Thus, soluble polymers may be loaded with substrates which are processed by polymer-anchored reagents or catalysts. At this stage, soluble impurities may be removed by polymer-bound scavenging reagents. Furthermore, prior to cleavage of the target molecule from the soluble resin, purification may be achieved by precipitation. More promising, however, is membrane filtration.

It is evident from the above discussion that the polymer supports used are still far from ideal in several respects and that there is considerable scope to prepare improved supports.^[246] Indeed, this is already a very active interdisciplinary area of research. The goal is to develop functionalized polymers and supports that have a satisfactory physical shape that permits agitation during reactions and filtration without problems. A reasonably high load capacity (>1.0 to 1.5 mmol g^{−1}), and repeat units that, unless required to do so, will not react with the diverse range of reagents involved in a multistage combinatorial synthesis are required. One way forward is to investigate beads prepared using cross-linking agents that are longer and more flexible than divinyl benzene. Such networks are likely to be superior to the common polystyrene beads.^[247] Related to this concept are tentagels which are a significant improvement. Here, the hydrophobic properties of cross-linked polystyrenes have been substantially offset by carrying out graft polymerization of ethylene oxide on the surface of the beads.^[248] At present, however, most tentagels show loading capacities (about 0.2 mmol g^{−1}) that are too low for use in stoichiometric transformations. Interestingly, magnetic separation techniques are slowly emerging in the field of solid-assisted organic chemistry;^[249] it has been shown that a ferromagnetic core can be encased in a highly cross-linked polymeric support. This technique gives beads which are enmeshed into larger composites composed of functionalized, 1–2% cross-linked polystyrene.^[250]

However, the most dramatic improvements in the design of ideal supports for reagents and catalysts, we think, will be seen in the field of macroporous inorganic materials.^[251] In general, inorganic supports do not tend to swell which makes them ideal supports for use in continuous reactors. Indeed, mesoporous phases based on zeolites, glass, and metal oxides, of which MCM-41 is the most prominent member, have appeared as highly promising supports in polymer-based synthesis,^[252] mainly as catalysts.^[253] These materials, prepared using surfactant micellar structures as templates, have a very

high surface area ($>1000\text{ m}^2\text{ g}^{-1}$). Techniques have been developed that allow construction of pores of highly defined size.^[254] These materials are composed of an ordered pore structure which is mostly an hexagonally packed array of inorganic tubules ranging from 20–100 Å in diameter. Remarkably, they show an extremely narrow pore-size distribution and the pore diameter can be adjusted from 2 to 15 nm. Co-condensation of reactive species during the mesopore synthesis is a method to incorporate functional groups into the walls of the channel system.^[255] Thus, organo-metallic complexes can be attached to the walls, which leads to the immobilization of catalysts originally designed for homogeneous catalysis.^[256] Reactions^[257] that have so far been conducted with these novel catalysts are the Heck-reaction,^[258] epoxidations,^[259] C–H activation,^[260] and Ziegler–Natta polymerization.^[261] This area develops ever faster, and recently the first stable organic analogue of a zeolite was prepared^[262] which showed catalytic properties in the base-catalyzed Knoevenagel condensation. In this remarkable work the authors employed lyotropic liquid crystals, which in an aqueous environment are organized in hexagonal channels. Depending on the amount of water used an inverted supramolecular structure is formed with the polar carboxylates directed into the channel in which the counterions are densely packed. These conglomerates were cross-linked in the presence of divinyl benzene which “froze” the cylindrical hexagonal structure.

In addition to these improvements, microfabricated systems^[263] will soon be used for combinatorial synthesis, including solution-phase synthesis promoted by functionalized polymers. The promise of miniaturization lies in the power of massive parallelization. Other potential benefits of miniaturization are automation, reduced waste streams, increased precision and accuracy, and disposability. Miniaturized reactors^[264] should be ideally suited for prederivatization of analytical and diagnostic samples and for microscale alteration of drugs and precious pharmacologically active natural products.

While this review was under preparation, several other examples of polymer-bound reagents appeared in the literature. These include polymer-attached aminium/uronium salts for peptide synthesis^[265] and polymer-supported thiophenol for removing excess alkylating agents from solution.^[266] In addition a lot of recently published work on functionalized polymers can be found in two recent reviews.^[267] We apologize to those investigators whose work could not be summarized herein.

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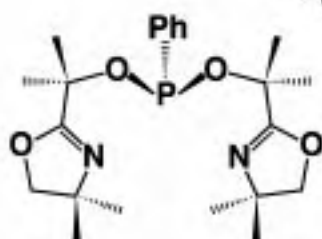
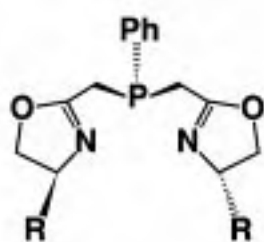
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metal-ligand interplay
hemilability ... hybrid ligands
phosphanyloxazolines
reversible coordination



sensors
dynamic behavior
homogeneous catalysis

Hemilability of Hybrid Ligands and the Coordination Chemistry of Oxazoline-Based Systems

Pierre Braunstein* and Frédéric Naud*

Dedicated to Professor Henri B. Kagan on the occasion of his 70th birthday

Ligand design is becoming an increasingly important part of the synthetic activity in chemistry. This is of course because of the subtle control that ligands exert on the metal center to which they are coordinated. Ligands which contain significantly different chemical functionalities, such as hard and soft donors, are often called hybrid ligands and find increasing use in molecular chemistry. Although the interplay between electronic and steric properties has long been recognized as essential in determining the chemical or physical properties of a complex, predictions remain very difficult, not only because of the considerable diversity encountered within the Periodic Table—different metal centers will behave differently towards the same ligand and different ligands can completely modify the chemistry of a given

metal—but also because of the small energy differences involved. New systems may—even through serendipity—allow the emergence of useful concepts that can gain general acceptance and help design molecular structures orientated towards a given property. The concept of ligand hemilability, which finds numerous illustrations with hybrid ligands, has gained increased acceptance and been found to be very useful in explaining the properties of metal complexes and in designing new systems for molecular activation, homogeneous catalysis, functional materials, or small-molecule sensing. In the field of homogeneous enantioselective catalysis, in which steric and/or electronic control of a metal-mediated process must occur in such a way that one stereoisomer is preferentially formed, ligands containing one or

more chiral oxazoline units have been found to be very valuable for a wide range of metal-catalyzed reactions. The incorporation of oxazoline moieties in multifunctional ligands of increasing complexity makes such ligands good candidates to display hemilabile properties, which until recently, had not been documented in oxazoline chemistry. Herein, we briefly recall the definition and scope of hemilabile ligands, present the main classes of ligands containing one or more oxazoline moieties, with an emphasis on hybrid ligands, and finally explain why the combination of these two facets of ligand design appears particularly promising.

Keywords: coordination chemistry • homogeneous catalysis • hybrid ligands • ligand design • sensors

1. Introduction

Recent years have witnessed considerable and increasingly fruitful activity in the two, originally independent, research areas of coordination and organometallic chemistry that we would like to combine and examine herein: the hemilability of polydentate hybrid ligands when coordinated to transition metals and the properties of complexes containing oxazoline-based ligands. The reasons for studying hemilabile ligands derives from their ability to provide open coordination sites at

the metal during reaction that are “masked” in the ground-state structure, and to stabilize reactive intermediates. Originally interest centered on reversible coordination, stoichiometric and catalytic activation, and transport of small molecules. Thus, metal complexes containing hemilabile ligands have been found to be catalytically active in a range of reactions, including hydrogenation, carbonylation or its reverse, hydroformylation of olefins and epoxides, allylation, epoxidation, olefin (co)dimerization and copolymerization and ring-opening metathesis polymerization (ROMP).^[1, 2] More recently, the activation of small molecules through reversible coordination to a metal center has been directed towards small-molecule sensing, in particular of CO.^[3, 4] The small energy differences, often in the order of 50 kJ mol⁻¹, involved in the dynamic processes which form the basis of hemilability, explains the difficulty, but also the chal-

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lenge, in designing systems endowed with specific properties. The concepts and analytical tools developed over the years in the context of molecular coordination and organometallic chemistry have stimulated new approaches in other disciplines, notably in heterogeneous catalysis, surface sciences, and bioinorganic chemistry. Although such aspects will not be discussed here, it is interesting to note that some metalloenzymes operate through a mechanism of activation similar to hemilability; for example, the opening of a zinc–cysteine bond allowing coordination of a water molecule occurs when going from an inactive to an active form of a metalloenzyme.^[5, 6] Furthermore, doubly functionalized porphyrins with imidazole-containing “arms” reversibly bind O₂ or CO through a hemilabile mechanism involving displacement of one imidazole arm.^[7] Hybrid ligands which contain significantly different chemical donor functions, such as hard and soft donor atoms or groups, find increasing use in molecular chemistry, largely because of their aptitude to display hemilabile behavior in the coordination sphere of a metal complex.

Oxazoline-based ligands have aroused considerable interest since their first use, in 1986, for asymmetric catalysis. They were used in the monophenylation of diols^[8, 9] and the hydrosilylation of ketones.^[10–12] The metal complexes used in asymmetric catalysis should contain a chiral ligand which sterically and/or electronically controls a metal-mediated

process in such a way that one stereoisomer is preferentially formed.^[13] Ligands containing one or more chiral oxazoline units have been found very useful for a wide range of metal-catalyzed reactions.

Herein, we would first like to briefly recall the definition and scope of hemilabile ligands and examine some extensions of this concept, then present the main classes of ligands containing one or more oxazoline moieties, and finally explain why the combination of these two categories of ligands appears particularly promising by summarizing some of our own recent results in this area.

2. Hemilabile Ligands

The transition metal coordination chemistry of hemilabile ligands has been recently presented in an excellent review article.^[1] We shall therefore focus here only on those aspects of hemilability that are relevant to the present discussion. The term “hemilabile” ligand was introduced about 20 years ago^[14] although the phenomenon itself had been observed earlier.^[15] The concept of ligand hemilability has since been used to encompass various situations; it is therefore necessary to briefly summarize what it now commonly covers.

Pierre Braunstein studied chemistry at the Ecole Supérieure de Chimie de Mulhouse, France, and after his Dr. Ing. in Strasbourg with Prof. J. Dehand, he was a postdoctoral fellow at University College London with Sir R. S. Nyholm and after his Doctorat d'Etat (Université Louis Pasteur), at the Technische Universität Munich with Prof. E. O. Fischer as an Alexander von Humboldt Fellow. He is Director of Research with the CNRS and the Director of the Coordination Chemistry Laboratory (UMR 7513 CNRS), University Louis Pasteur, Strasbourg. His main research interests are in the inorganic and organometallic chemistry of the transition and main group elements where he is author or coauthor of over 290 scientific publications and review articles. He is an associate editor of “New Journal of Chemistry” and of “Dalton Transactions” and serves (or has served) on the board of numerous international journals. He is a Corresponding Member of the French Académie des Sciences (Paris) and a Fellow of the Royal Society of Chemistry and has received various awards including the Alexander von Humboldt research award (1988), the CNRS Silver Medal (1989), the Max-Planck Research Award (1991), the Raymond Beer Prize of the French Chemical Society (1995), the first Paul Sabatier-Miguel Catalá award (1998) and the Victor Grignard–Georg Wittig award (1999).



P. Braunstein

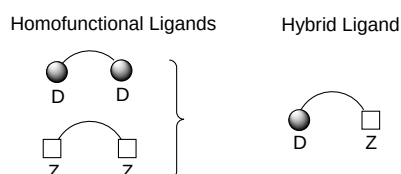


F. Naud

Frédéric Naud received his Maitrise from the Université de Poitiers, during these studies he joined the laboratory of Prof. J. A. Burke at Trinity University, San Antonio, Texas as summer undergraduate research student in 1993 and 1994. He obtained his Diplôme d'Etudes Approfondies in 1995 from the Université Louis Pasteur, Strasbourg, working in the laboratory of Dr. P. Braunstein on the chemistry of functional phosphanes. He was then a research associate, for 15 months, with Prof. M. D. Fryzuk, University of British Columbia, Vancouver, in a cooperation program on the synthesis of phosphorus oxazoline-based ligands. Back in Strasbourg in the Laboratoire de Chimie de Coordination, he obtained his PhD in 1999 for his work on the coordination and catalytic properties of metal complexes bearing phosphorus oxazoline-based ligands. In the course of this work, in 1998, he joined the group of Prof. A. Pfaltz at the Max-Planck Institut für Kohlenforschung, Mülheim/Ruhr, Germany for 3 months, a team which he latter rejoined in 2000 as a post-doctoral fellow at the University of Basel, Switzerland. He currently holds a research position at Solvias AG, Basel, working in the field of asymmetric catalysis.

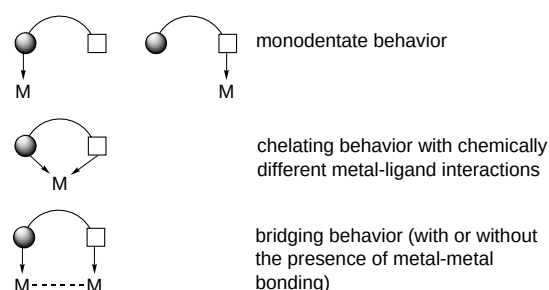
2.1. Definitions

Hybrid ligands are polydentate ligands that contain at least two different types of chemical functionality capable of binding to metal centers (Scheme 1). These functionalities



Scheme 1. A hybrid ligand contains at least two chemically different donor functions.

are often chosen to be very different from each other to increase the differentiation between their resulting interactions with the metal center(s) and thereby their chemo-selectivity (Scheme 2). In turn, these functionalities will



Scheme 2. Bonding modes of hybrid ligands.

influence the bonding/reactivity of the other ligands bound to the metal, in particular those in the *trans* position. Combining hard and soft donors in the same ligand—often called a hybrid or heteroditopic ligand^[2]—has represented one of the greatest endeavors, the hope being that different and contrasting chemistries could be associated within the same molecule, thus leading to novel and unprecedented properties for the resulting metal complexes.

An essential feature of hemilabile ligands is to have at least one substitutionally labile donor function Z while the other donor group(s) D remain firmly bound to the metal center(s). They were first encountered in mononuclear complexes where numerous examples have now been identified, but the concept of hemilability can easily be extended to dinuclear complexes,^[16] and metal clusters^[17, 18] where the labile coordination site does not need to be at the metal ligated by the strong donor D but could be at an adjacent metal site (Scheme 2). The lability which leads to selective breaking of the Z→metal interaction in a mononuclear, dinuclear, or cluster complex may occur under different circumstances (Scheme 3). Type I corresponds to the spontaneous “opening” of the $\widehat{DZ}$ chelate (mononuclear system) or bridge (di- or polynuclear system), type II to the intramolecular competition with another donor function and type III to the coordination of an external reagent. The latter obviously applies equally to dinuclear or cluster complexes, for simplicity these

have not been represented in Scheme 3. These various possibilities will be detailed in Section 2.2.

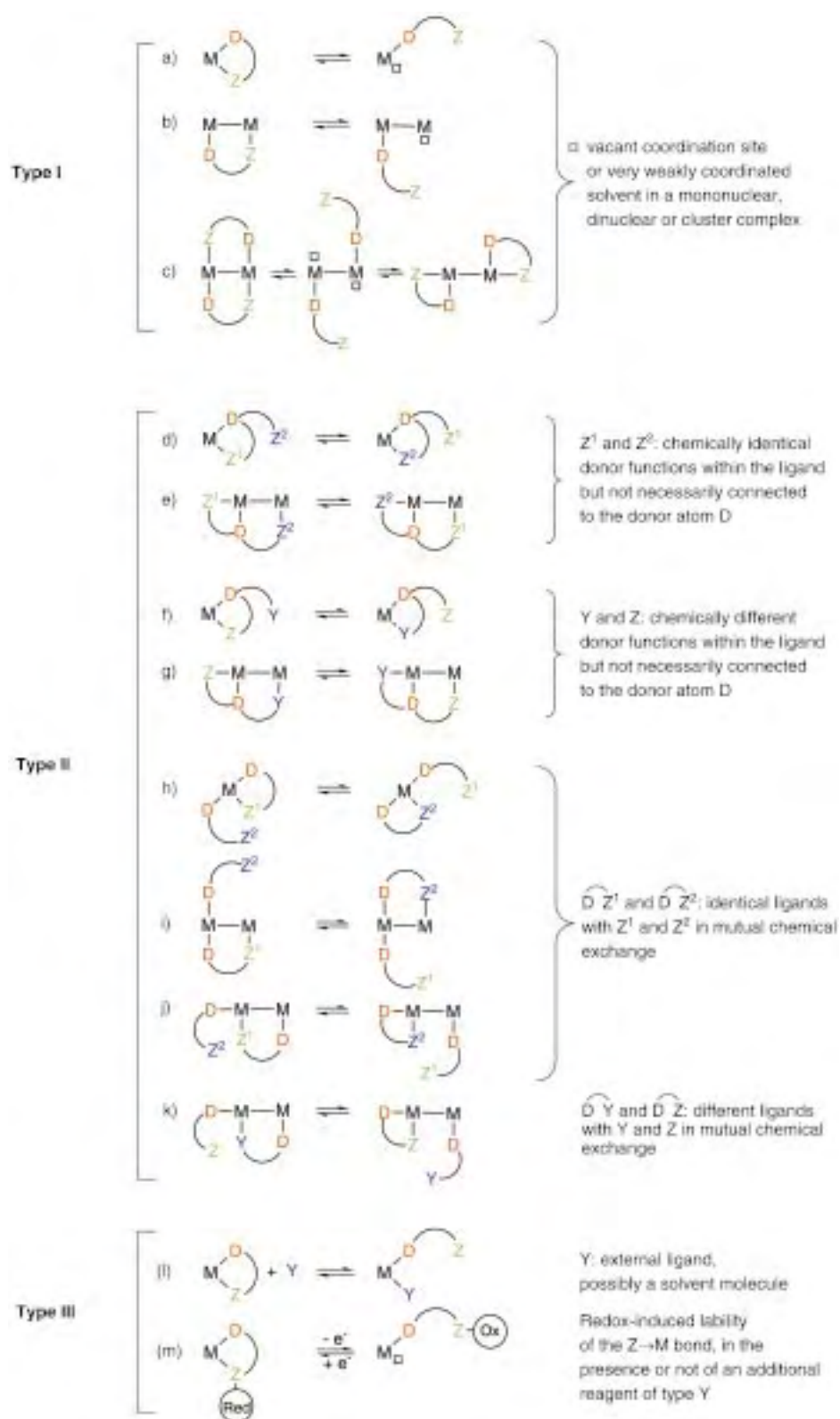
Although symmetrical, homofunctional bidentate ligands such as $\text{Ph}_2\text{PCH}_2\text{PPh}_2$ or $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2$ may also change their coordination mode from bridging or chelating to monodentate or vice versa, such systems should not be categorized as hemilabile ligands since the resulting metal–donor interactions are not intrinsically different, in contrast to the situations in Scheme 2. If these donor groups behave differently, this will be the result of the presence at the metal center of other chemically different ligands, for example in a position *trans* to the metal–donor interaction concerned.

We suggest that another essential criterion to consider before assigning hemilabile character to a ligand is the reversibility of the formation/displacement of the $Z \rightarrow \text{metal}$ interaction. Although this may appear somewhat restrictive since in an irreversible “opening” of a chelating ligand $\widehat{DZ}$ to give a $\widehat{ZD} \rightarrow M$ monodentate system, “half” (“hemi”) of the ligand was indeed labile. Our limitation emphasizes the importance of having relatively small energy differences between the “open” and “closed” situations, which should be an important property of hemilabile ligands. The irreversible “opening” or “closing” of a chelate with or without participation of an external reagent is of course a sign of reactivity, but not of hemilability in the sense that we wish to use herein. This is like comparing a wind–screen wiper with a single cleaning sweep!

2.2. Occurrence of Hemilability

After the opening of the $Z \rightarrow \text{metal}$ bond has taken place, recoordination of the Z functionality may restore the original situation, as typically observed in fluxional processes (e.g. in Scheme 3a and b), or in the reversible binding of a small molecule (Scheme 3 part I). Recoordination may also take place after a chemical transformation has occurred within the metal coordination sphere. Thus for example, decoordination of the Z functionality may allow—or result from—fixation of a small molecule like CO to a metal alkyl complex which may lead to migratory insertion and formation of an acyl ligand. This transformation liberates a coordination site to which the function Z can coordinate. Alternatively, the migratory–insertion step may be promoted by the entropically favored tendency of the $\widehat{DZ}$ ligand to chelate the metal center (Scheme 4). Note that a possible consequence of the chelating ability of the $\widehat{DZ}$ ligand is to force the newly formed ligand to adopt a position in the final complex different from that expected on the basis of the mechanism of the elementary step concerned, for example, CO insertion versus alkyl migration (Scheme 4). Such an example will be described in Section 2.2.1.

As indicated in Section 2.1, the presence of a hemilabile ligand in a complex may significantly influence the reactivity of incoming substrates and promote transformations that would not otherwise occur. Such an example is presented in Scheme 5. Whereas the complexes *trans,cis,cis*- $[\text{RuCl}_2(\eta^2\text{-P}_2\text{O})_2]$ ($\text{P}_2\text{O} = i\text{Pr}_2\text{PCH}_2\text{CH}_2\text{OMe}$, $i\text{Pr}_2\text{PCH}_2\text{C}(\text{O})\text{OMe}$) react with $\text{HC}\equiv\text{CPh}$ to give the vinylidene complexes $[\text{RuCl}_2(\eta^1\text{-P}_2\text{O})(\eta^2\text{-P}_2\text{O})(=\text{C}=\text{CHPh})]$ in which one of the P_2O chelates



Scheme 3. Various hemilabile situations. Type III extends to dinuclear or cluster complexes.

has opened to provide a coordination site for the vinylidene unit, related Ru^{II} complexes with the ligand $\text{P}(\text{O})\text{Pr}_3$ instead of $\text{P}(\text{O})\text{Pr}_3$ do not perform this isomerization.^[19] The rapid intramolecular exchange in the chelating behavior of the two $\text{P}(\text{O})\text{Pr}_3$ ligands (Scheme 3h) is characterized by a free enthalpy of

activation of 41 and 53 kJ mol^{-1} , for the ether and ester phosphanes, respectively.

It was recently suggested that the cycloreversion process of **1** that leads to complexes **3** and **4** (Scheme 6) occurs via intermediate **2**, with a decoordinated phosphane sidearm.^[20a] Reoordination of the phosphane would liberate either CO or diphenylethyne. This is consistent with the observation that **3** does not undergo a thermal ligand-exchange process with diphenylethyne to give **4**.

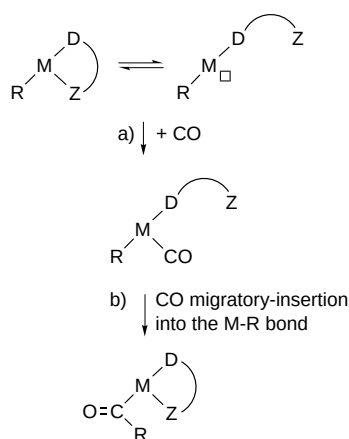
Numerous other examples have been reported in recent years of cyclopentadienyl-based hemilabile ligands where, for example, an olefin, amine, phosphane, ether, or thioether function tethered to the ring reversibly coordinates to the metal center in the presence of an external substrate (Scheme 3l).^[1, 20b] This often leads to dramatic rate enhancements in catalytic reactions, as exemplified in ethylene polymerization with Cr, Ti, and rare-earth metal complexes.^[21, 22]

Other types of labile donor functions that are often involved in hemilabile behavior are E-H groups which can form agostic bonds to the central metal atom, in most cases E is carbon. This type of bonding plays a central role in olefin polymerization (Scheme 7) where coordination of the monomer is facilitated by the easy opening of the β -agostic bond involving the growing alkyl chain.^[23] An early example was reported for half-sandwich Co^{II} complexes.^[24, 25]

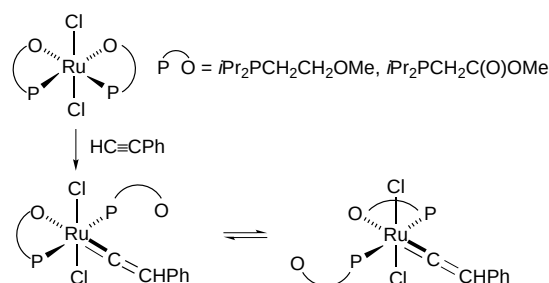
The sequence of events shown in Scheme 4 is typical of that found in numerous catalytic cycles, this further emphasizes the significance of hemilabile ligands in homogeneous or supported catalysis where the “opening” step allows coordination, activation, and transformation of a substrate molecule at the metal site while the “closing” step leads

to stabilization of the metal coordination sphere and favors elimination of the product.^[1, 2, 26–28]

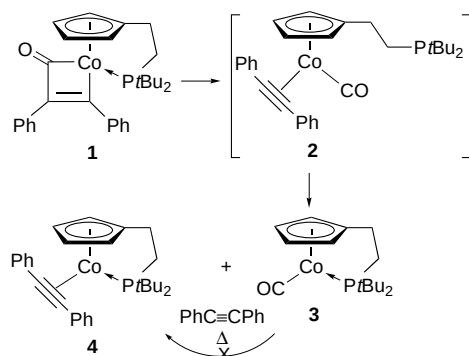
Furthermore, the “opening and closing” mechanism is not restricted to the precursor or product of a reaction but may also occur in the intermediate species. Thus, it was shown by



Scheme 4. The steps of CO coordination a) can initiate the “opening” of the chelate ring or take place on the vacant site created by spontaneous “opening”. The CO migratory-insertion step b) may occur spontaneously and be followed by “closing” of the chelate or, alternatively, may be triggered by it.

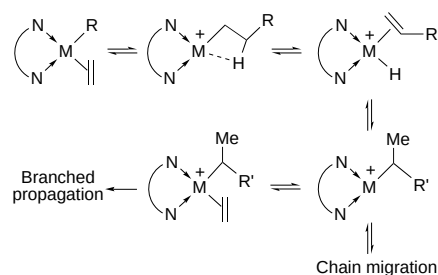


Scheme 5. Reactions with organic substrates may be promoted by hemilabile P,O ligands. Whereas $[RuHCl(CO)(PiPr_3)_2]$, for example, does not convert $HC\equiv CPh$ into the corresponding vinylidene complex $[Ru=C=CHPh]$, this transformation is possible when ether–phosphane or ester–phosphane ligands are used.^[19]



Scheme 6. Cycloreversion reaction of the cobaltacyclobutenone chelate complex **1** leading to complexes **3** and **4** via intermediate **2** with a decoordinated phosphane sidearm.^[20]

Shaw et al. that the oxidative addition of MeI to Ir^I complexes of the type $[IrCl(CO)(PR_3)_2]$ was about 100 times faster with the phosphane ligand $PMe_2(o-MeOC_6H_4)$ than with PMe_2Ph or $PMe_2(p-MeOC_6H_4)$.^[29] It was suggested that the *ortho*-methoxy group can temporarily coordinate to Ir^I , thus making the metal center more electron-rich, thereby facilitating the oxidative-addition reaction (“anchimeric assistance”; Scheme 8). An electronic effect acting through the phosphorus was ruled out for $PMe_2(o-MeOC_6H_4)$ by comparison with



Scheme 7. Involvement of β -agostic $C-H \cdots M$ interactions in the mechanism of ethylene polymerization with Ni and Pd α -diimine complexes.^[23]

$PMe_2(p-MeOC_6H_4)$ since electronic effects should be more pronounced with the latter ligand. Interestingly, in the ground-state structure of the precursor Ir^I complex and the Ir^{III} product, the $PMe_2(o-MeOC_6H_4)$ ligand was exclusively P-bound to the metal center.

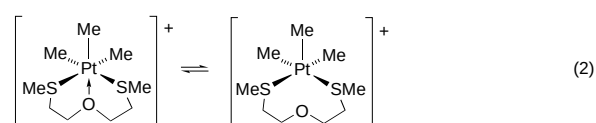
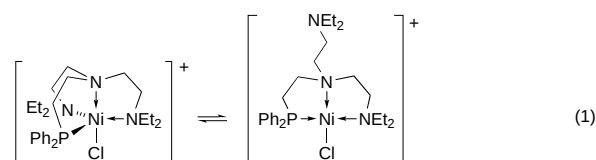
In organolithium chemistry a hemilabile amino ether ligand has been shown to impart, among other things, dramatic rate accelerations in lithium diisopropylamide (LDA) mediated dehydrohalogenations or α - and β -eliminations of epoxides.^[30, 31] This acceleration was related to the behavior of the difunctional ligand which forms a weakly coordinated monodentate linkage in the reactant but a strongly coordinated bidentate linkage in the transition structure which stabilizes this species.

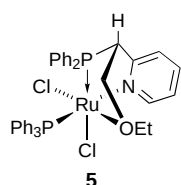
Ligand hemilability has recently been used to control catalyst turnover frequency and enantioselectivity in the alkylation of aldehydes.^[32]

Let us now briefly examine the various categories of hemilabile behavior depicted in Scheme 3.

2.2.1. Type (I) Hemilability

The situations in Scheme 3a–c are typically encountered with metal centers which have easily variable coordination numbers: $3 \rightleftharpoons 2$ (e.g. d^{10} ML_3/ML_2 complexes), $4 \rightleftharpoons 3$ (e.g. d^8 ML_4/ML_3 complexes), $5 \rightleftharpoons 4$ (e.g. d^8 ML_5/ML_4 complexes), and $6 \rightleftharpoons 5$ (e.g. d^6 ML_6/ML_5 complexes). Ligands other than bidentate ones can of course give rise to such hemilabile behavior and examples of the reversible change in coordination number from 5 to 4 and from 6 to 5 are shown in Equations (1)^[33] and (2),^[34] respectively.

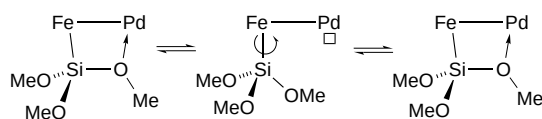




A further example is provided by the Ru^{II} complex **5** which contains an optically active P,N,O ligand. The hemilabile behavior was detected by variable-temperature NMR spectroscopy.^[35] Quite surprisingly, it is the pyridyl ring that reversibly coordinates to the metal center and not the harder ether function.

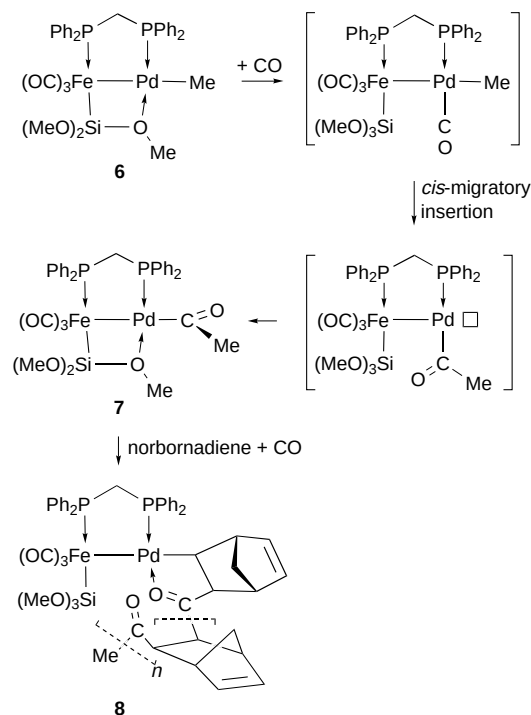
This could be explained by the higher *trans* influence of the PPh₃ ligand compared to that of the chloride ion.

Ligand hemilability in dimetallic complexes (Scheme 3b), is exemplified by the dynamic behavior of the bridging trimethoxysilyl ligand in a number of Fe–Pd complexes. The equivalence of the OMe protons on the NMR time scale was explained by rapid “rotation” of the Si(OMe)₃ ligand about the Fe–Si axis.^[16, 36] Below coalescence temperature the complex was static (Scheme 9).



Scheme 9. Formation and dynamic behavior of a $\eta^2\text{-}\mu_2\text{-Si-O}$ interaction (the ancillary ligands are omitted for clarity).

The hemilability of the trimethoxysilyl ligand results in the existence of a “masked” coordination site at the Pd center in complex **6** accessible to small molecules that may coordinate, sometimes reversibly, to the metal center (Scheme 10). If the spontaneous opening of the O → Pd bond had not been detected in solution by variable-temperature NMR spectroscopy,



Scheme 10. “Opening” and “closing” steps of the $\eta^2\text{-}\mu_2\text{-Si-O}$ bridge during sequential CO/olefin insertion.

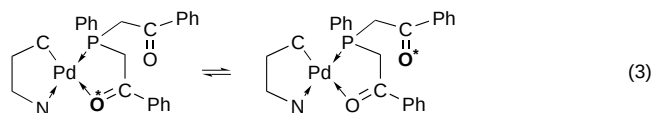
copy, one could argue that reversible coordination of a small molecule would actually correspond to a situation of type (III) where an external reagent triggers the opening of the O → Pd bond. The readily available coordination site at the Pd center has been exploited for the coordination of small molecules like isonitriles, CO, or olefins and has led to the formation of poly(iminomethylenes)^[37] and polyketones resulting from the alternating insertion of CO and olefins into a palladium–carbon bond (Scheme 10).^[37, 38]

By design, the CO molecule has to occupy a coordination site *cis* to the alkyl group in such complexes, which facilitates the migratory-insertion step. It was shown by trapping experiments that the resulting acyl ligand is originally *trans* to the PPh₂ group and then flips to a position *trans* to the metal–metal bond in **7**.^[16, 39] This isomerization allows (or was induced by) recoordination of the methoxy oxygen atom to the palladium center. Insertion of an olefin into the metal–acyl bond may then occur. This reaction results in the reopening of the SiO → Pd bond, driven by the chelation of the carbonyl group and leading to a five-membered chelate which is preferred over the four-membered $\mu_2\text{-}\eta^2\text{-Si-O}$ bridge. Since CO insertion into the metal–alkyl bond is faster than olefin insertion, a new metal–acyl bond forms which restores a situation similar to that in **7**. However, CO insertion into a metal–acyl bond is thermodynamically unfavorable, so an olefin molecule inserts into the metal–acyl bond to give a metal–alkyl bond, into which a CO inserts, and so on. This leads to the growth of a perfectly alternating polyketone chain in **8**. Such polyketones are of considerable current interest,^[40–48] as demonstrated with the commercial developments of Carilon^[49, 50] by Shell and Ketonex^[51, 52] by BP Chemicals.^[53] The lability of the SiO → Pd bond in related Fe–Pd complexes has also been invoked to explain the considerable catalytic activity of some of these dimetallic complexes for the dehydrogenative coupling of stannanes.^[54, 55]

In Scheme 3c two bridging hybrid ligands convert into two chelates as a result of the spontaneous opening of the Z → M bonds.

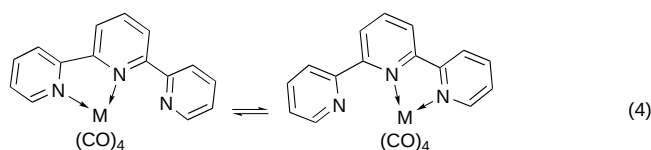
2.2.2. Type (II) Hemilability

In the following examples, intramolecular competition between donor functions is responsible for ligand hemilability. In Scheme 3d, the hemilability of the chelate is associated with an intramolecular fluxional process that may be frozen at lower temperature.^[56–59] An example is given in Equation (3) where above the coalescence temperature the two carbonyl



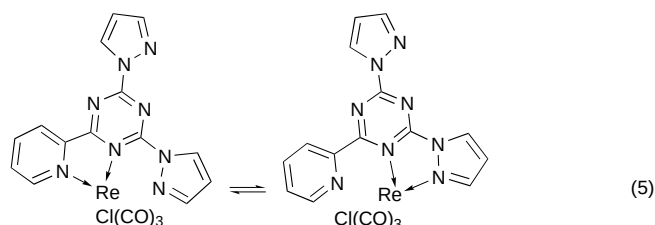
groups of the phosphane ligand bind alternately to the Pd center.^[60, 61] The mutual exchange of the two carbonyl functions is facilitated by the proximity of the uncoordinated one while the phosphorus donor serves as an anchor.

Another example of this type of fluxional process is provided by the pyridine-group exchange observed with the terpyridine ligand in tetracarbonyl complexes $[M(CO)_4\text{-}(\text{terpy-}N,N)]$ ($M = \text{Mo}, \text{W}$) [Eq. (4)].^[62] The latter dynamic behavior has been termed a “tick-tock twist”.

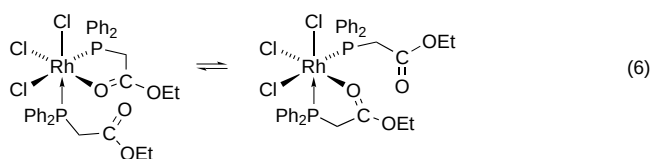


Scheme 3e shows an exchange between two chemically identical arms of a hybrid ligand that may act as a chelate or a bridge between two metal centers.

The reactions in Scheme 3f and 3g require a suitable trifunctional ligand and have therefore been less frequently studied or observed.^[63] An example is given in Equation (5)^[64, 65] and a further one can be found later [Eq. (18)].^[66]



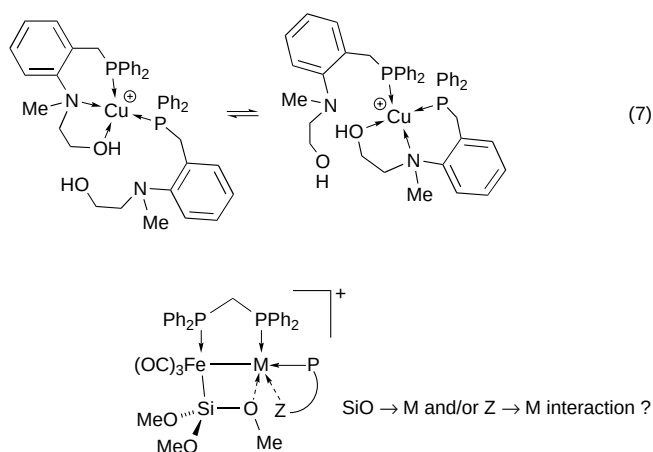
The reaction in Scheme 3h involves two independent but identical ligands in mutual intramolecular exchange owing to the lability of their Z function. This phenomenon was recognized at a very early stage in studies on hybrid ligands and an example is illustrated in Equation (6).^[15]



Most systems in this category involve two or more hemilabile hybrid ligands interacting with one metal center.^[27, 67, 68] The resulting dynamic situation has often been described in terms of a “wind-screen wiper” mechanism.^[69] A recent example involving a P,N,O tridentate ligand and the complexation of a Cu^+ ion is shown in Equation (7).^[70]

In Scheme 3i and 3j the reactions follow a similar pattern but involve two different metal centers.

The situation in Scheme 3k has been examined recently for two chemically different hemilabile ligands (with the donor atoms D being Si and P, respectively) which carry different oxygen functionalities able to compete for the same coordination site, as shown in Scheme 11.^[71]

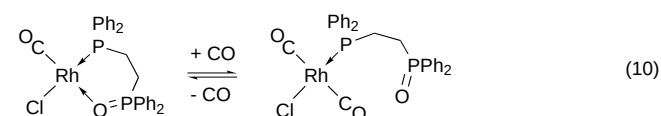
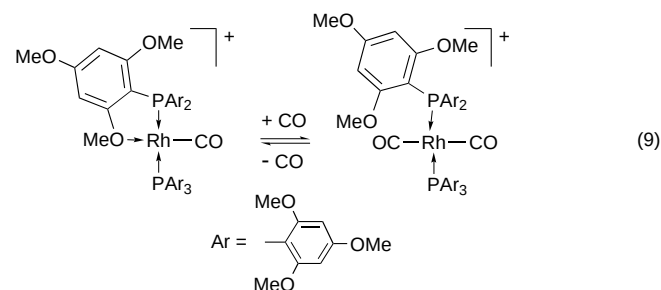
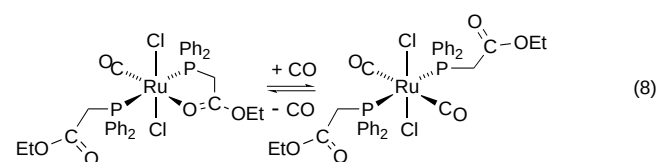


Scheme 11. Possible competition between labile donor groups for a coordination site at M. $\bar{P}\bar{Z}$ = various hybrid phosphane ligands; M = Pd or Pt.

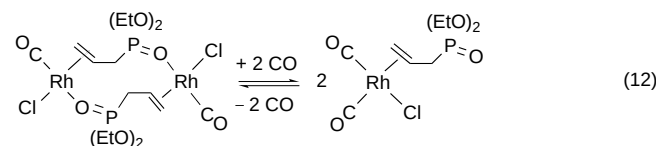
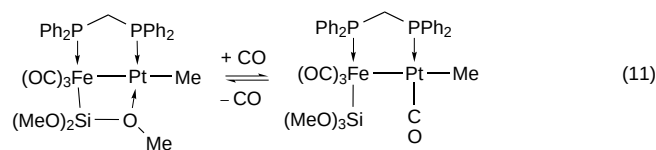
2.2.3. Type (III) Hemilability

In these examples, an external reagent Y, which can be electrons in the case of redox reactions, is involved in the breaking of the labile ligand–metal bond. The reaction in Scheme 3 part I covers a range of possibilities depending on the nature of Y. Systems where the external reagent Y is a small molecule, such as CO, which, depending on its partial pressure can reversibly coordinate to the metal, are illustrated in Equations (8)–(10).^[3, 4, 26, 72, 73]

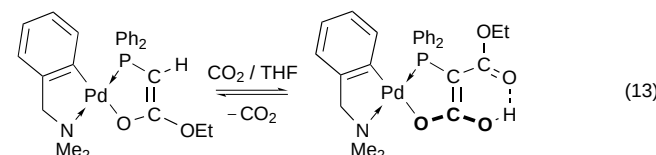
The Rh system shown in Equation (10) was used as a catalyst in methanol carbonylation.^[26] It is interesting that the analogous P,S ligand did not show any hemilabile behavior but gave rise to enhanced catalysis, showing that other effects are at work.^[74–76] Further reactions of the kind shown in Sche-



me 31 come from the dimetallic chemistry of hemilabile $\text{Si}(\text{OMe})_3$ ligands^[77] or from dinuclear complexes with bridging allylphosphonate ligands^[78, 79] [Eq. (11) and (12)].



Finally, the possibility to promote an “opening and closing” type situation from a nondynamic chelate by the reversible reaction of the metal complex with an external reagent is worth mentioning. This is illustrated in Equation (13) by a

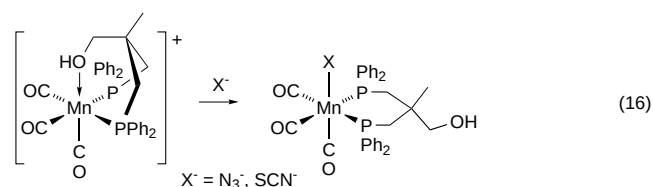
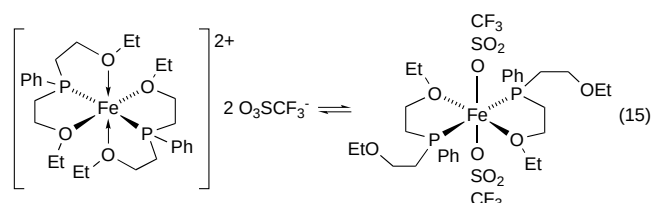
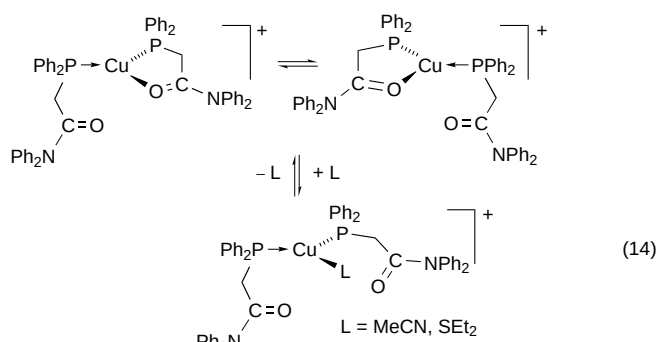


palladium complex which reversibly binds CO_2 , under ambient conditions, with the formation of a C–C bond.^[80] The phosphino ester enolate ligand in the precursor acts as a three-electron donor and coordinates through the P and O atoms to form a stable chelate ring. However, after incorporation of CO_2 , a new P,O chelate is formed in which the O–Pd bond is reversibly cleaved when CO_2 is eliminated. This restores the original O–Pd bond. Therefore, the reversible opening of the O–Pd bond is entirely because of the external reagent, although the chemical nature of this oxygen function changes during the reaction.

The reversible uptake of small molecules (e.g. CO , CO_2 , SO_2) may be used as a means to “detect” them in the gas phase and can be applied in molecular sensors.^[3, 4, 28, 81, 82] Thus, for example, the Rh^{I} phosphane–ether complex in Equation (9) was incorporated into thin films and shown by optical-based sensing to selectively and reversibly coordinate CO in the presence of O_2 , CO_2 , N_2 , and H_2 under ambient conditions.^[3, 4]

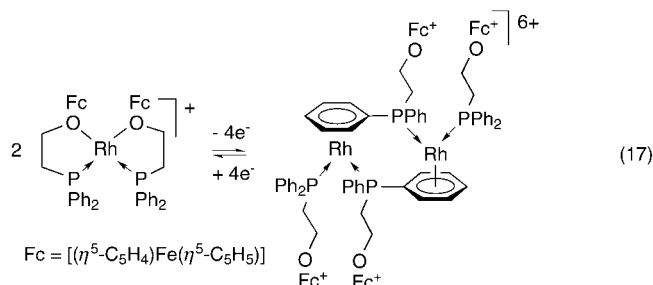
A solvent molecule may also displace the kinetically more labile $\text{Z} \rightarrow \text{M}$ bond, as shown with the Cu^{I} complexes in Equation (14).^[83] In the absence of a donor solvent, only hemilabile behavior of the type shown in Scheme 3h is observed. By exploiting their spectroscopic properties, Ru^{II} bipyridyl complexes containing a hemilabile phosphane ether ligand have been used as sensors for molecules such as DMSO, MeCN, or SMe_2 .^[84]

Furthermore, Y may also represent a potentially coordinating counter ion that can compete with a donor function and displace it reversibly from the metal center. This is exemplified by the displacement of the oxygen arm of a P,O,O ligand [Eq. (15)]^[85] and of a P,P,O ligand in [Eq. (16)].^[86]



Bischelated P,N aminophosphane Pt^{II} complexes that exhibit in vitro activity against cisplatin-resistant tumor cells readily attack the DNA base thymine through a chelate ring-opening mechanism. It was shown that the latter can be controlled by the substituents on the N atom, the size of the chelate ring, the pH, and the concentration of an external reagent such as the Cl^- ion.^[87]

Finally, functional ligands with a redox-active center may exhibit a hemilabile behavior of the type shown in Scheme 3h, as in Cu^{I} complexes with the ferrocenyl ketophosphane ligand $[\text{Ph}_2\text{PCH}_2\text{C}(\text{O})\text{Fc}]$ **9** (Fc = ferrocenyl),^[79] or an electron-transfer induced hemilability of the type in Scheme 3m, as encountered in a recently developed class of so-called “redox switchable” ligands [Eq. (17)].^[88]



Potential applications of redox-switchable hemilabile ligands include the development of new catalysts the reactivity of which may be tuned by the redox active centers, the preparation of electroactive films for metal complexation, and

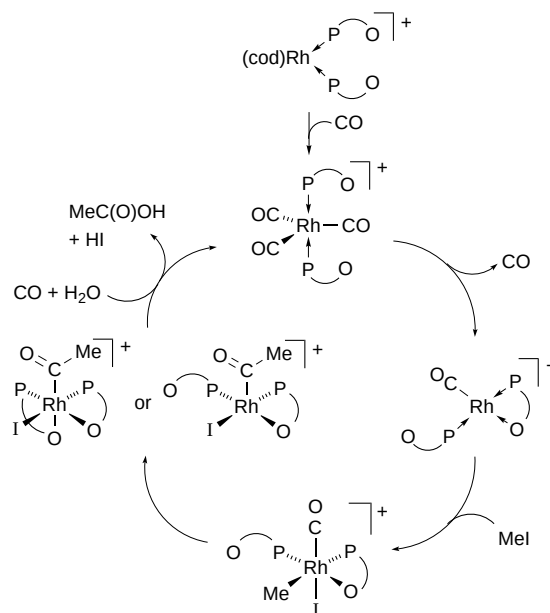
the synthesis of novel materials for molecule separation technologies.^[1, 88, 89]

Considering the ubiquitous role of phosphorus-based ligands in coordination and organometallic chemistry, it is not surprising that the most investigated class of hemilabile ligands is that of functional phosphanes.

2.3. Hemilabile Functional Phosphanes

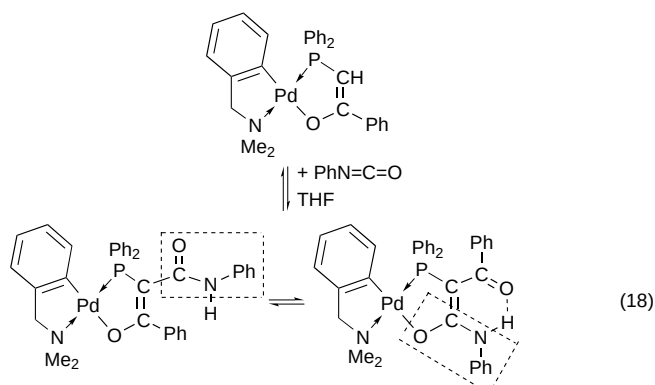
Endowed with soft and hard donor groups, phosphorus–oxygen and phosphorus–nitrogen based ligands represent the most studied class of functional phosphanes and many such examples have been presented in the previous section. The oxygen functional groups associated with the phosphorus donor come from alcohol, ether, ketone, ester, amide, and phosphane oxide or phosphonate groups.^[1, 2, 26, 27, 43, 78, 90–94] Although these various functions will impart significant changes in the coordination properties and hemilability of the corresponding P,O ligands, it is generally observed that phosphorus–oxygen ligands are the most weakly chelating type of ligand. It is therefore not surprising that their complexes have been utilized in homogeneous and supported catalysis (by anchoring onto solid supports or sol–gel processing),^[28] where temporary protection and facile generation of vacant, reactive sites at the metal centers constitute a prerequisite. Successful catalysis was observed in reactions such as the carbonylation of methanol into acetic acid and methylacetate (Co, Rh), the hydrocarbonylation of methanol into acetaldehyde using synthesis gas (Co, Rh), hydrovinylation (Ni), hydrogenation of aldehydes and ROMP (Ru), hydrogenation of (prochiral) alkenes and alkynes (Rh), hydroformylation (Rh), and ethylene/CO copolymerization (Pd). An example of a catalytic cycle showing how the opening and closing mechanism involving P,O ligands facilitates the elementary steps involved (oxidative addition, methyl migration) is shown in Scheme 12 for ether–phosphane ligands such as $R_2PCH_2CH_2OMe$ ($R = Ph, nPr$).^[2]

A specific class of P,O ligands, the phosphino enolate and related types, has been shown to confer very interesting properties to their metal complexes. They can behave as spectator ligands as in organonickel(II) complexes which contain three-electron-donor anionic P,O chelates such as $[Ph_2PCH_2C(O)O]^-$ or $[Ph_2PCH=C(O)Ph]^-$ and which are efficient catalyst precursors for the highly selective oligomerization of ethylene into linear α -olefins, a reaction which forms the basis of the industrial Shell Higher Olefin Process (SHOP).^[95–102] However, the postulated mechanism of this catalytic reaction does not imply hemilabile behavior of the P,O chelate but instead involves a hydrido nickel species of the type $NiH(P,O)$ which is electronically unsaturated and allows the coordination and subsequent insertion of ethylene.^[96, 97, 103] In palladium(II) chemistry such anionic P,O chelates may also behave as reactive moieties towards a wide range of electrophilic organic or inorganic reagents. In these cases, the covalent $Pd-O_{enolate}$ bond does not display any lability.^[66, 80, 104–109] However, an example of a hemilabile phosphino enolate ligand was found in the course of reactivity



Scheme 12. Carbonylation of MeI catalyzed by ether–phosphane rhodium complexes.^[2a]

studies on palladium(II) complexes with organic isocyanates which led to new multifunctional systems [Eq. (18)].^[66] The hemilability of the new ligand corresponds to the situation in Scheme 3 f. It is noteworthy that a substitutionally inert



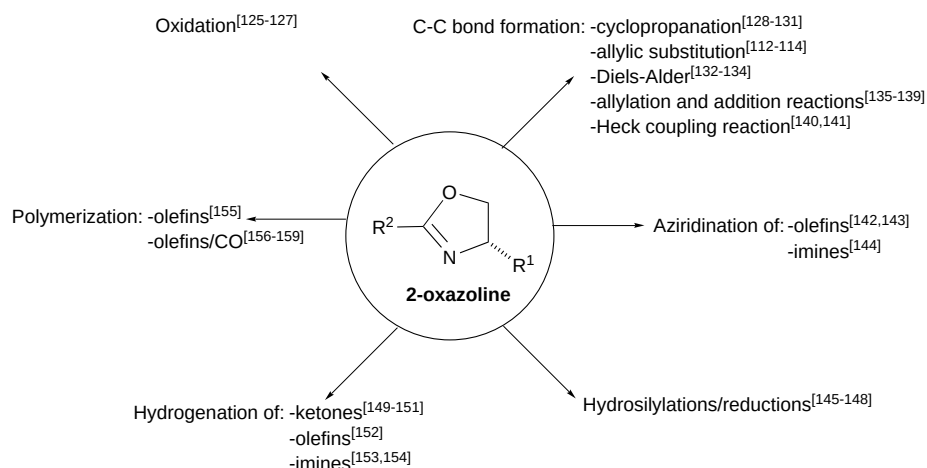
palladium–oxygen bond can acquire hemilabile character after appropriate chemical transformations. A related phenomenon was described above in Equation (13).

Amine and pyridine moieties are the most common donors associated with phosphorus–nitrogen ligands but amides, imines, or nitriles have also been used as the weakly coordinating end of P,N chelates.^[110] These hybrid ligands often display hemilabile behavior but it is generally observed that the lability of the nitrogen moiety is lower than that of the oxygen moiety of P,O ligands. However, the beneficial effect of P,N ligands, for example, on the rhodium-catalyzed hydroformylation of olefins is documented.^[111]

The dominant position of P,O and P,N donors in studies on hybrid and hemilabile ligands contrasts with the absence, to the best of our knowledge, of studies describing the dynamic behavior of phosphane-oxazoline ligands, which could in

principle behave as P₂O or P₃N donors. This is even more surprising when one considers the increasingly successful use of phosphane-oxazoline chelates in organometallic chemistry and homogeneous catalysis.^[112–115]

We would now like to address this point and examine some of our own results on the coordination properties of tridentate phosphane-oxazoline ligands and analyze the conditions that lead to their hemilabile behavior.



Scheme 13. Applications of oxazoline-based ligands in homogeneous catalysis.

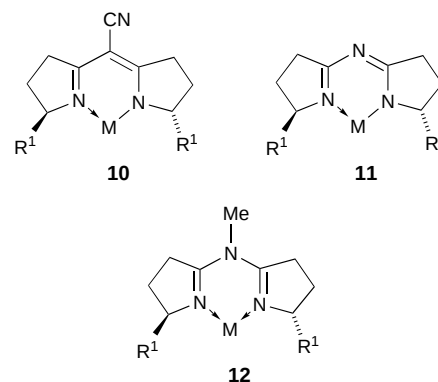
3. Oxazoline-Based Ligands

Metal-catalyzed asymmetric synthesis is a powerful tool since large amounts of optically active products can be synthesized using a small amount of optically active catalyst.^[116–121] Most of these catalysts are metal complexes containing a chiral organic ligand which sterically and/or electronically controls a metal-mediated process in such a way that one stereoisomer is preferentially formed.^[13]

It is only since 1986 that oxazoline-based ligands have been used in asymmetric catalysis, originally for the monophenyl-ation of diols^[8, 9] and later the hydrosilylation of ketones.^[10–12] This initiated considerable research activity in the field and triggered the synthesis of numerous chiral ligands containing at least one oxazoline structural unit.^[122–124] In a short space of time these ligands have been used successfully in many metal-catalyzed reactions. The stability of oxazolines towards hydrolysis and oxidation is a great advantage compared to phosphanes which are readily converted into phosphane oxides in reactions carried out under (slightly) oxidative conditions. The number of applications is steadily growing and a less than exhaustive list is given in Scheme 13.

Oxazoline units are expected to readily coordinate a metal center and they have indeed been shown to bind to a wide range of transition metals (Scheme 14).

The successful use of oxazoline-based ligands was paralleled by that of semicorrin ligands (see **10–12**),^[123, 177] the first examples of which were also published in 1986.^[178] The advantage of these ligands is that the two stereogenic centers

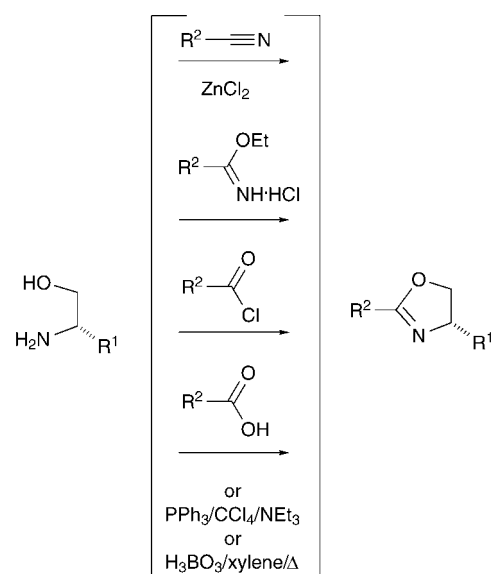


are held in close proximity to the metal and thus have a strong and direct influence on the stereochemical course of a metal-catalyzed process.

Semicorrin ligands were successfully applied to the copper-catalyzed cyclopropanation of olefins and the cobalt-catalyzed conjugate reduction of α,β -unsaturated carboxylic esters and amides. The related structure of oxazoline compared to semicorrin prompted several research groups to investigate the synthesis and the potential of bis(oxazoline) ligands in asymmetric catalysis. One major advantage that such ligands offer the synthetic chemist is that chiral oxazolines can readily be prepared in enantiomerically pure form from simple precursors (chiral pool; Scheme 15).^[179] In fact, various optically pure amino alcohols are commercially

Sc	Ti [147,160 161]	V [125,162]	Cr	Mn [165]	Fe [122b,167]	Co [122b,124, 143]	Ni [165,170]	Cu [122b,128, 132,175,176]	Zn [135, 137]
Y	Zr [155]	Nb	Mo [58,163, 164]	Tc	Ru [126,130, 149,151]	Rh [145,146, 168,169]	Pd [131,136, 143, 169, 171]	Ag	Cd
La	Hf [155]	Ta	W [163]	Re [58,166]	Os	Ir [153,154]	Pt [172,173]	Au [174]	Hg

Scheme 14. Oxazoline donor ligands coordinate to a wide range of transition metals, those in italics (references given in parenthesis).



Scheme 15. Preparation of enantiomerically pure oxazolines from readily available precursors.

available (e.g. $R^1 = i\text{Pr}$, $s\text{Bu}$, $t\text{Bu}$, Me , Ph) or can be readily prepared by reduction of the corresponding α -amino acids.^[180, 181] Using these methods several chiral oxazoline-based ligands have been synthesized. They can be divided into two main classes: 1) neutral ligands, which behave as electron donors but also as π acceptors and can bind electrophilic, cationic metal centers, and 2) anionic ligands with stronger electron-donating properties, which can reduce the electrophilicity of a metal ion or allow coordination to early transition metals. Oxazoline-based cationic ligands have been far less developed (see Section 3.3).

3.1. Oxazoline-Based Neutral Ligands

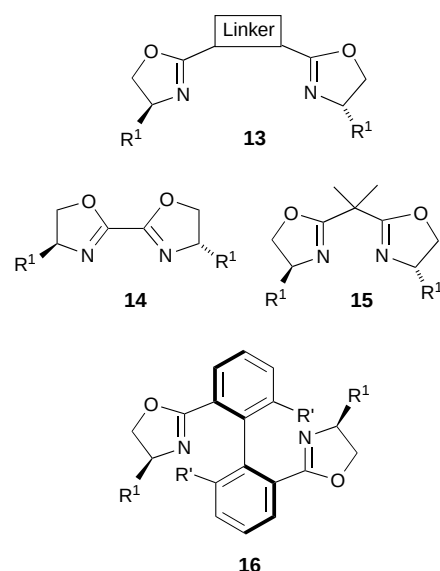
Most oxazoline-based ligands belong to this class and it is possible to distinguish them according to their potential coordination behavior, namely monodentate, bidentate, tridentate, and multidentate.

3.1.1. Monodentate Behavior

Although monodentate oxazolines have been encountered in coordination chemistry,^[182] it is only very recently that a monodentate chiral oxazoline has been used in metal-catalyzed asymmetric synthesis. This first example concerned a nickel-catalyzed multicomponent tandem coupling.^[183]

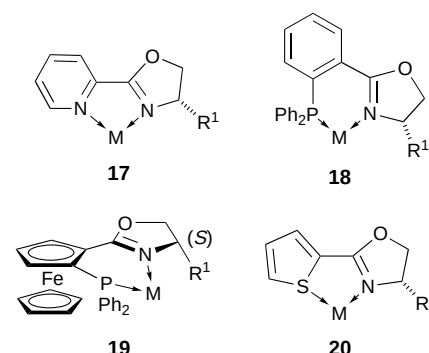
3.1.2. Bidentate Behavior

Owing to the excellent results obtained with semicorrin ligands, many C_2 symmetric bidentate bis(oxazoline) ligands have been synthesized to vary the nature, size, and flexibility of the link between the oxazoline moieties and also the nature of the substituent (R^1) held by the oxazoline stereogenic center (see **13**). A selection is depicted below, ligands **14**–**16**.



A recent review by Gosh et al.^[124] nicely summarizes the different C_2 ligands reported and their use in various metal-catalyzed asymmetric syntheses.

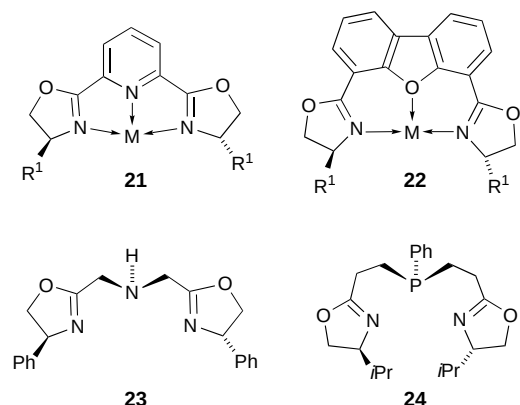
As seen above with other heterofunctional ligands, increased selectivity can be induced by the (stereo)electronic properties of the donor atoms. This applies to heterofunctional N,N' ligands such as **17**^[10, 184] and to P,N **18**,^[115] **19**,^[150, 151] or S,N **20** ligands^[185, 186] and has resulted in the high enantioselectivities obtained in asymmetric allylic alkylation with Pd complexes bearing the P,N ligand **18**.^[112–114]



3.1.3. Tridentate Behavior

Several research groups have taken advantage of the versatility of the oxazoline synthesis to introduce a donor atom into the link between the oxazoline rings to give a potentially tridentate ligand. It is anticipated that the tridentate ligands will form a deeper chiral concave pocket around the metal center than the corresponding chiral bidentate ligands. This has led to the development of several ligands, among these Nishiyama's tridentate bis(oxazoline) "Pybox" system **21** which has been particularly useful (e.g. for the asymmetric hydrosilylation of ketones and the cyclopropanation of olefins).^[130, 145, 187] In systems **21** and **22** the planarity of the link allows only a meridional (*mer*) coordination mode of the ligand, while in **23** and **24**, the sp^3 character

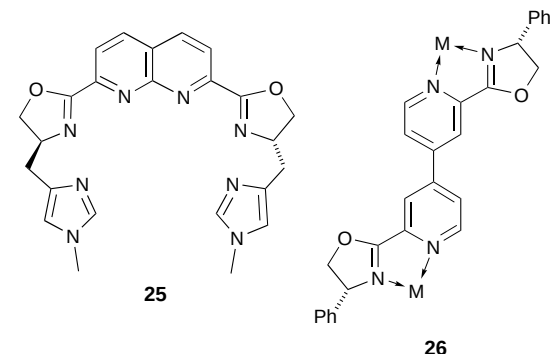
of the donor atom combined with the flexibility of the backbone is expected to allow both *mer* and facial (*fac*) coordination modes. No coordination chemistry has been



reported for **23** and **24** although these ligands allow good to excellent activities and enantioselectivities in ruthenium-catalyzed asymmetric transfer hydrogenation reactions.^[188, 189]

3.1.4. Multidentate Behavior

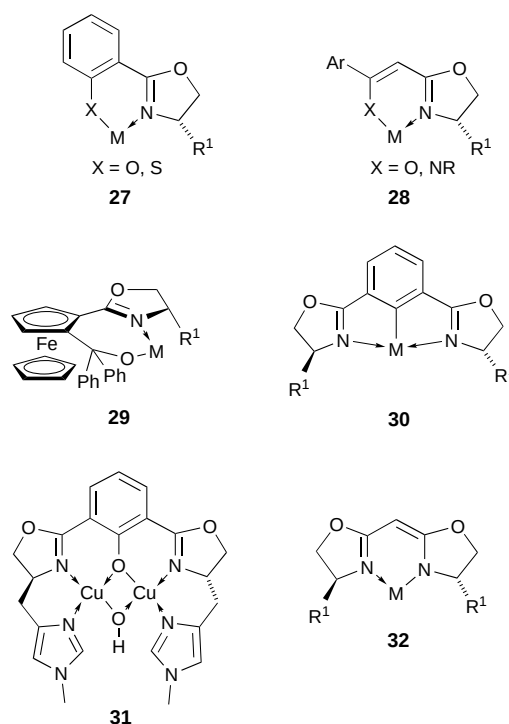
Interest is also growing in the design of polydentate ligands such as **25**^[190, 191] and **26**^[146] which could form di- and polynuclear complexes.



Recent studies indicate the considerable potential that dinuclear and cluster complexes have for catalysis,^[192] and for modeling the catalytic activity of metalloenzymes.^[193] Several examples demonstrate that dinuclear metal complexes can display distinct advantages over mononuclear metal catalysts and mixed-metal systems offer the additional potential of selective activation of two different substrates.^[192, 194] Such complexes can mediate multielectron transfers,^[195] activate a substrate by simultaneous coordination to two (or more) metal centers^[196, 197] or, in the case where metal–metal bonding is present, allow direct insertion of a substrate into such a bond, a process that does not require ligand dissociation to generate coordinative unsaturation.^[198] Although the potential of multidentate oxazoline-based ligands is obvious, reports describing their use are still limited.

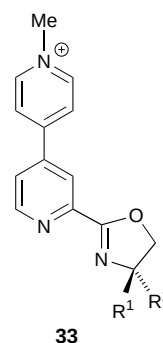
3.2. Oxazoline-Based Anionic Ligands

Chiral anionic ligands containing oxazolines have been prepared to allow the fine tuning of the electronic properties of the metal center, and also to strengthen the complexation by creating a covalent bond between the metal and the ligand.^[169, 172] This class of ligands has allowed the preparation of very efficient catalysts^[129, 136, 138] although there are fewer examples of such ligands than of their neutral analogues. As with the neutral ligands, the anionic ligands can be divided into several families according to their potential coordination behavior. An important additional feature which allows differentiation is whether the anionic charge is carried by an external atom as in systems such as **27**,^[125, 160, 162, 165, 199, 200] **28**,^[143] **29**,^[137, 138] **30**,^[131, 169, 172] **31**,^[191] or on the pyrrole nitrogen of pyrrole oxazolines,^[201] or largely localized on the oxazoline nitrogen atom as in **32**.^[128, 129, 136, 147, 161, 168, 202] A further example will be shown below with **40**.^[210, 211]



3.3. Oxazoline-Based Cationic Ligands

With the hope of preorganizing the electron-donating substrate in the Rh^I-catalyzed enantioselective hydrosilylation by charge-transfer effects, the electron-accepting ligand **33** has been prepared.^[203]

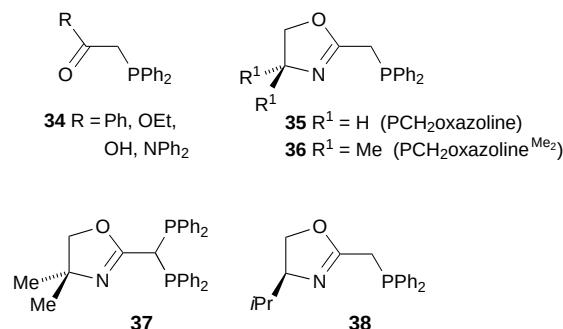


4. Hemilabile Phosphorus–Oxazoline Hybrid Ligands

4.1. Bidentate P,N Ligands

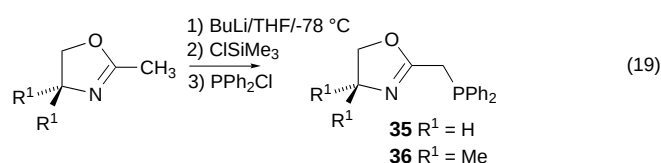
As an extension of our studies on the coordination chemistry of, and catalysis with, the ligands β -phosphino-

ketones,^[67, 204–206] -ester,^[15] -acids, or -amides,^[83, 90] of type **34**, we became interested in using oxazoline moieties for the design of new functional phosphane ligands.



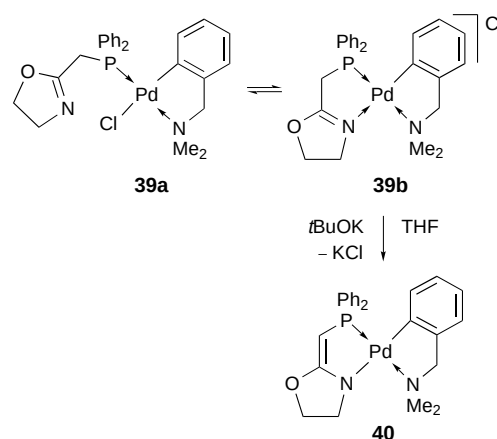
Our first approach was to synthesize P,N ligands (**35** and **36**) analogous to the P,O type ligand **34** by a similar method which involved the reaction of the carbanion derived from 2-methyl-2-oxazoline with PPh₂Cl. This approach failed because of the deprotonation of the expected monophosphorylated product by the oxazoline carbanion present in solution, which resulted in the formation of a diphosphorylated oxazoline ligand **37** among other products.^[207, 208]

We then adapted a one-pot procedure recently described by Helmchen et al. for the preparation of **38** which consists first of the deprotonation of the corresponding 2-methyl-2-oxazoline in THF at -78°C , followed by the addition at this temperature of Me₃SiCl to form the *N*-silyl derivative which finally reacts with PPh₂Cl as shown in Equation (19).



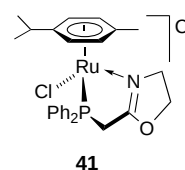
To examine the coordination properties of the new ligands, we first considered four-coordinate palladium(II) complexes and generally observed the formation of stable P,N chelates in complexes such as [PdMe(Cl)(PCH₂oxazoline)] and [PdMe(SMe₂)(PCH₂oxazoline)](O₃SCF₃) with the ligand PCH₂oxazoline.^[207] The bidentate coordination of the ligand strongly differentiates the positions *trans* to P and N. Thus, as observed in the copolymerization of CO and ethylene, the ligand induces a mutual *cis* arrangement of the incoming substrate and the growing polymeric chain. Opening of the chelate is possible and upon reaction of two equivalents of PCH₂oxazoline with one equivalent of [[Pd(dmba)(*u*-Cl)]₂], (dmba = *N*-benzyltrimethylamine) the species **39a** and **39b** were found to be in rapid equilibrium in solution (Scheme 16).^[211]

This behavior corresponds to the hemilability in Scheme 31 and it was clearly established by the presence in the IR spectrum of **39** in CH₂Cl₂ of two vibration bands assigned to coordinated and uncoordinated oxazoline moieties. This



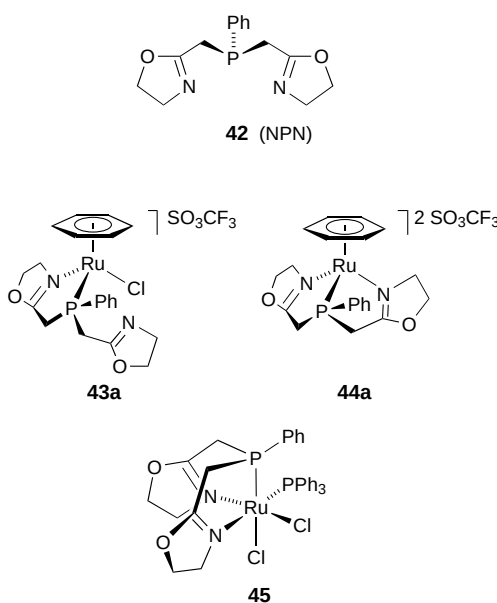
Scheme 16. Hemilabile behavior of the PCH₂oxazoline ligand in **39** and transformation into the stable chelate complexes **40** upon deprotonation.

dynamic situation is suppressed upon deprotonation of the PCH₂ group which gives in **40** a static, three-electron-donor anionic chelating ligand (Scheme 16).^[210, 211] In contrast to **39**, the PCH₂oxazoline ligand in compound **41** does not exhibit any hemilabile behavior although the chloride counterion could have occupied a coordination site on the Ru center. This situation illustrates how the coordination mode of the phosphinooxazoline ligand is tuned by the choice of the metal center.



4.2. Tridentate N,P,N and Related Ligands

Since the PCH₂oxazoline ligand seemed to preferentially form strong chelates and is fairly inert toward competition from external ligands, we introduced with the new N,P,N ligand bis(oxazoliny)(phenyl)phosphane (**42**, NPN) the possibility of an intramolecular competition between two equivalent oxazoline arms within the same ligand (Scheme 3d).^[208]

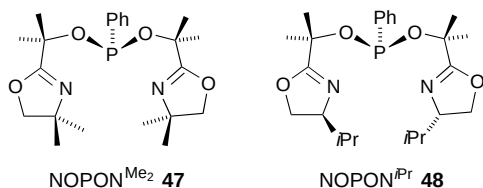


Surprisingly, the NPN ligand in complex **43a** behaves only as a static N,P chelate. Removal of the chloride by treatment with $\text{Ag}(\text{O}_3\text{SCF}_3)$ led to the expected chelation of the pendent arm of the ligand giving compound **44a**.^[208] This tridentate bonding mode is also observed in complex **45** where NPN coordinates in a *fac* manner. This coordination mode seems to be preferred to *mer* since varying the Ru precursors and the reaction conditions (solvent, temperature) led only to the formation of complexes containing NPN in either *fac* (**45**) or pseudo-*fac* geometry (**44a**).

Owing to the increasing interest in new catalysts that allow hydrogenation reactions under mild conditions and preferably in the absence of hydrogen gas,^[212, 213] complex **45** was tested for the transfer hydrogenation of acetophenone in propan-2-ol. This complex is a very active catalyst precursor which gives yields of phenethylalcohol up to 97% and turnover frequencies as high as $112\,000\text{ h}^{-1}$.^[208]

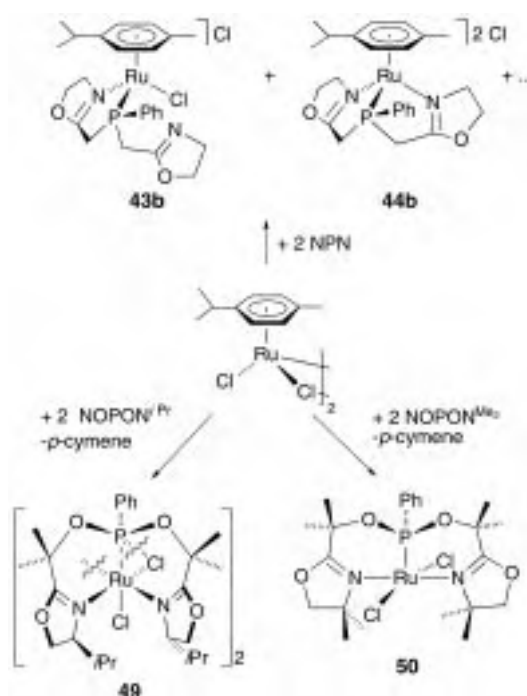
Note that Heard et al. examined the coordination properties of Nishiyama's Pybox ligand in hexacoordinated Pt, Re, Mo, and W complexes. They found evidence for a dynamic process where the bidentate bonding mode of Pybox in **46** is associated with a fluxional exchange of pendent and coordinated oxazolines.^[58, 166] This process occurs according to a "tick-tock twist" [see Eq. (4)] and/or a "rotation" mechanism. Thus, comparing our bis(oxazolinyl)-(phenyl)phosphane ligand **42** to the Pybox ligand, it can be seen that a change in the nature of the donor atom of the linker between the two oxazolines (sp^2 -hybridized N vs. sp^3 -hybridized P in **42**), although keeping the same chelate size, leads to different coordination behavior.

We then designed a new ligand, larger than NPN, anticipating that a longer link between the phosphorus and oxazoline units would offer more flexibility and thus allow a *mer* coordination mode. The new bis(oxazoline)(phenyl)phosphonite ligands, **47** and **48**, were prepared by the reaction



of two equivalents of the corresponding 2-(α -hydroxyalkyl)-2-oxazolines with one equivalent of PPhCl_2 in the presence of excess NEt_3 .^[214] The complexation of these new NOPON ligands to Ru^{II} centers differs from that of the NPN ligands and is influenced by the substituents on the oxazolin ring: the reactions in Scheme 17, performed under identical conditions (6 h, THF, reflux), show that depending upon the ligand used three different products can be obtained.

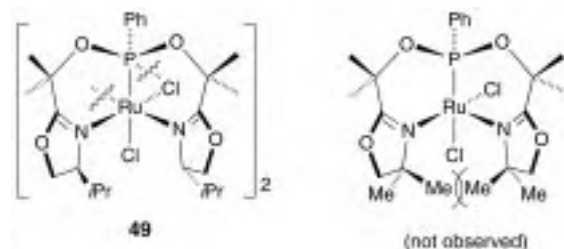
In contrast to the bis(oxazolinyl)(phenyl)phosphonite ligands, NPN did not displace the *p*-cymene ligand from Ru^{II}



Scheme 17. Contrasting behavior of the ligands NPN, NOPON^{Me2}, and NOPON^{iPr} in Ru^{II} complexes.

but formed monocationic (**43b**) and dicationic (**44b**) complexes in which NPN displays bidentate or tridentate coordination, respectively. Therefore, the size of the chelate (five vs. six-membered) and/or the nature of the phosphorus donor atom (phosphonite vs. phosphane) appears to play an important role for the substitution of the *p*-cymene ligand. Furthermore, the nature of the oxazoline substituents in NOPON^{Me2} and NOPON^{iPr} must be considered to explain their different coordination behavior. NOPON^{Me2} (**47**) gives *mer* tridentate coordination in a pentacoordinate, square-pyramidal complex **50** while NOPON^{iPr} (**48**) gives *fac* tridentate coordination in a hexacoordinate dinuclear complex **49**. In **47** both oxazolin rings each have two methyl substituents at the C4 atom whereas **48** has only an isopropyl group at the *S*-configured C4 center. Thus in ligand **48** if two oxazolines are placed in close proximity, as in a *fac* coordination mode, the *iPr* groups can avoid each other. Whereas if **47** was to adopt a *fac* coordination mode, two of the four methyl groups would point towards each other and thus create an unfavorable steric clash (Scheme 18).

This is not the case in the *mer* situation. Moreover, the fact that no compound of the type $[\text{RuCl}_2(\text{mer-NOPON}^{\text{iPr}})]$ could

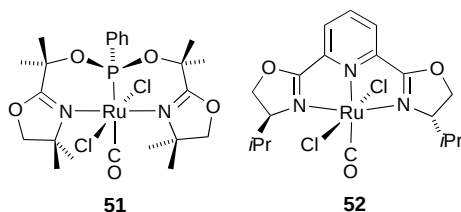


Scheme 18. The presence of two methyl groups on the oxazoline C4 center prevents facial coordination of the NOPON^{Me2} ligand.

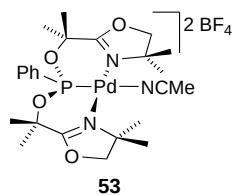
be detected indicates that, when given the choice, this new class of ligands prefers to bind in a *fac* coordination mode.

Compound **49** represents a rare example of a fully characterized complex where a tridentate chiral bis(oxazoline) ligand coordinates in a nonmeridional fashion. We performed preliminary studies for the asymmetric transfer hydrogenation of acetophenone in propan-2-ol and obtained a conversion of 98% with 26% *ee* of the secondary alcohol product.^[214]

Bubbling CO into a solution of complexes $[\{\text{Ru}(\mu\text{-Cl})\text{Cl}(\text{NOPON}^{\text{tPr}})\}_2]$ (**49**) and $[\text{RuCl}_2(\text{NOPON}^{\text{Me}_2})]$ (**50**) leads to carbonyl complexes in which the carbonyl group is incorporated into to the vacant sixth coordination site or by opening of the chloride bridge, respectively. No further coordination of CO occurs, consistent with the stability of the tridentate *mer* or *fac* coordination modes. Comparison between the IR data for the $\nu(\text{CO})$ vibration and between the chemical behavior of CO in $[\text{RuCl}_2(\text{CO})(\text{NOPON}^{\text{Me}_2})]$ (**51**)^[214] and $[\text{RuCl}_2(\text{CO})(\text{Pybox}^{\text{tPr}})]$ (**52**)^[130] indicates that the Ru–CO bond in **51** is weaker than that in **52**, because the *trans* influence of the P donor in $\text{NOPON}^{\text{Me}_2}$ is greater than that of the N donor in the Pybox ligand. This difference underlines the importance of the electronic effects induced by the multidonor ligand on the reactivity of the complex.

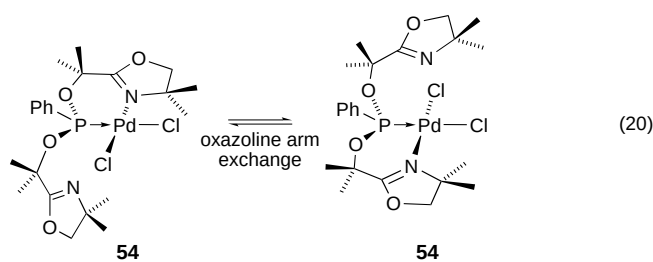


As the hemilabile behavior of the $\text{PCH}_2\text{oxazoline}$ ligand is strongly dependent on the metal center, the Pd chemistry of $\text{NOPON}^{\text{Me}_2}$ was examined.^[209] Again the difference between NPN and $\text{NOPON}^{\text{Me}_2}$ is striking since while reaction of $\text{NOPON}^{\text{Me}_2}$ with $[\text{Pd}(\text{NCMe})_4](\text{BF}_4)_2$ cleanly afforded compound **53**, reaction with NPN under similar conditions led to the formation of uncharacterized products. Interestingly, excess acetonitrile did not dissociate one arm of the oxazoline ligand from the Pd center in **53**.

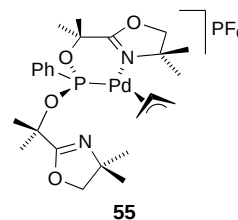


The bis(oxazoline)(phenyl)phosphonite ligand in compound **54** exhibits a dynamic bidentate coordination mode where the two oxazoline arms exchange rapidly as shown by variable-temperature NMR spectroscopy [Eq. (20)].^[209]

This dynamic process corresponds to the hemilability shown in Scheme 3d and prompted us to investigate the behavior of $\text{NOPON}^{\text{Me}_2}$ complexes in which an additional ligand can also display changes in hapticity. The allyl ligand which can easily adopt either η^1 - or η^3 -bonding modes appeared to be the candidate of choice.^[215] The η^3 -bonding

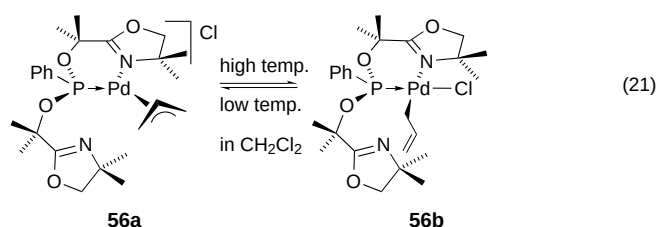


mode is the most generally observed case while η^1 -allyl complexes have been isolated mainly with platinum^[216–218] or early transition metals.^[219–221] The manner in which an allyl fragment coordinates to a transition metal center and its ability to change its coordination geometry will influence the stereochemistry of reactions proceeding via allyl intermediates.^[215, 222] For instance, it is well known in palladium–allyl chemistry that an η^3 - η^1 - η^3 mechanism may operate and that it can be either detrimental to or favorable for enantioselectivity. Therefore, it appears important to recognize the bonding mode of an allyl ligand in a (catalytic) system to understand or rationalize its reactivity. Many Pd–allyl complexes with an η^3 -coordination mode of the allyl unit have been isolated. Only a few Pd complexes containing η^1 -allyl ligands have been reported although they are either the reactive species or the proposed intermediates in C–C coupling reactions. To study the mutual influence of the allyl and $\text{NOPON}^{\text{Me}_2}$ ligands, we first investigated the allyl complex **55** obtained from the reaction of $\text{NOPON}^{\text{Me}_2}$ with 0.5 equivalents of $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)(\mu\text{-Cl})_2]$ and one equivalent of NH_4PF_6 . This compound displays behavior similar to that of $[\text{PdCl}_2(\text{NOPON}^{\text{Me}_2}\text{-N,P})]$ in that the oxazoline N donors of the dynamic bidentate-coordinated ligand are continually exchanging with one another. The allyl ligand remains coordinated in an η^3 fashion over the temperature range 200–395 K. Thus, in contrast to literature reports on the chemistry of Pd–allyl complexes with P,N,N and N,N,N ligands,^[223, 224] we could not isolate a complex of the type $[\text{Pd}(\eta^1\text{-C}_3\text{H}_5)(\text{NOPON}^{\text{Me}_2}\text{-N,P,N})]^+$.

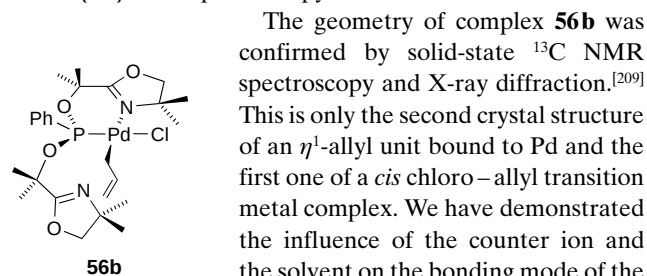


We then examined the situation where the chloride ligand from the Pd precursor ($[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)(\mu\text{-Cl})_2]$) is not replaced by the PF_6^- ion and could therefore influence the dynamic behavior of the ligands by coordination to the metal. The complex thus obtained (**56**) exhibits, under the same conditions as for **55**, fluxional behavior of the allyl ligand, as indicated by variable-temperature ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopy. Again spectroscopic data show that $\text{NOPON}^{\text{Me}_2}$ is a dynamic N,P chelate, while the additional fluxional behavior of the allyl unit is related to the presence of the chloride ion [Eq. (21)].^[209]

This competition between the η^3 -bonding mode of the allyl and the coordination of the Cl^- ion, meets the requirements of reversible opening and low energy cost for a hemilabile situation of the type in Scheme 31, although strictly speaking this qualification is not appropriate since an η^3 -bonded allyl



ligand has two identical terminal carbons. It also appears that the dynamic behavior depends on the solvent since changing from CH_2Cl_2 to toluene displaces the equilibrium towards a complex with a static η^1 -bonded allyl ligand as detected by ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopy at 260 K.



56b
in toluene solution and
in the solid state

The geometry of complex **56b** was confirmed by solid-state ^{13}C NMR spectroscopy and X-ray diffraction.^[209] This is only the second crystal structure of an η^1 -allyl unit bound to Pd and the first one of a *cis* chloro-allyl transition metal complex. We have demonstrated the influence of the counter ion and the solvent on the bonding mode of the allyl unit, a key feature for the stereoselectivity observed in asymmetric allylic substitution reactions where ion

and solvent effects have a significant influence on the rate and enantioselectivity of the reaction.^[225, 226] It is unclear whether the hemilabile $\text{NOPON}^{\text{Me}_2}\text{-N,P}$ chelate is or is not a simple spectator ligand. The relative positions and mutual influence of the η^1 -allyl and the chloride ligands seen in this complex have not been observed with bidentate ligands, including phosphinoaryl-oxazolines^[112, 113] and phosphinoferrocenyl-oxazolines.^[227] This ligand arrangement has however been invoked for intermediates proposed in the dynamic processes of η^3 -allyl palladium complexes.^[228]

In conclusion, it was found that (phosphinomethyl)oxazoline ligands do not always behave as stable chelates as often assumed but may exhibit hemilabile behavior. This was established for a situation where the oxazoline nitrogen competes with an external donor ligand, such as chloride, for coordination sites. This situation results in a hemilabile behavior of the type shown in Scheme 31 and is suppressed when the external donor ligand is removed. Such ligand-competition reactions are of course dependent on the nature of the metal center and of the ancillary ligands. This is illustrated by the comparative behavior of the $\text{PCH}_2\text{oxazoline}$ ligand in Pd complexes **39** and Ru complex **41**; only in **39** could an external chloride ion compete with the N-donor ligand for a coordination site.

For a study of hemilabile behavior of the type shown in Scheme 3d, the N,P,N ligand **42** was designed which contains two identical oxazoline arms. Surprisingly, this ligand was found to adopt only *fac* tridentate or static bidentate coordination modes. No opening/closing mechanism resulting from competition between these two arms was observed.

The new bis(oxazoline)(phenyl)phosphonite ligand **47** was prepared and found to adopt either static *fac* or *mer* tridentate coordination modes or a dynamic bidentate hemilabile

behavior as shown in Scheme 3d. The introduction of a chiral oxazoline as in **48** alters the coordination properties and leads exclusively to *fac* tridentate coordination. Obviously the size of the chelate ring and the nature of the P donor atom play a crucial role in the occurrence of hemilability. In the presence of an external donor ligand like chloride, which has a tendency to coordinate to the metal center, one could have expected an enhanced dynamic behavior that could parallel that described above with **39**. However the reaction shown in [Eq. (21)] provided an unexpected result because the external chloride triggered the coordination of the allyl ligand in a terminal η^1 mode while the $\text{NOPON}^{\text{Me}_2}$ ligand remained bidentate. This led to the stabilization of the first *cis* η^1 -allyl chloride transition metal complex.^[209]

5. Conclusion

The hemilability of hybrid ligands is a property that attracts increasing interest as documented by the current research efforts aimed at understanding its occurrence and scope. The diversity of situations encountered and illustrated in Scheme 3 also indicates the number of parameters and the subtlety with which they need to be tuned for this phenomenon to occur. The importance of hemilability was first demonstrated in homogeneous catalysis where it continues to provide new and exciting results. More recently ligand hemilability has also been applied to the development of new molecular-based sensors and materials. The introduction of oxazoline moieties in hybrid ligands has opened the door to studies on their involvement in hemilabile systems that can readily carry and transfer chiral information. It can be anticipated that such studies will continue to provide new and exciting results.

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Does CIP Nomenclature Adequately Handle Molecules with Multiple Stereoelements? A Case Study of Vancomycin and Cognates**

K. C. Nicolaou,* Christopher N. C. Boddy, and Jay S. Siegel*

The Cahn–Ingold–Prelog (CIP) system^[1–3] is the prevalent set of rules and conventions governing the nomenclature of chemical compounds. Given its simple premise, the CIP system does a remarkable job of providing useful configurational assignments even for molecules with a large number of tetrahedral stereocenters. In an attempt to be generally applicable to the naming of all compounds, stereoelements such as axes and planes were invented and codified.^[1] The strict identification of these elements and the conventions for assigning their configurations has been far less “user friendly” than the simple regular tetrahedral stereocenter. Not only has the existence of the whole class of “planar” elements been obviated,^[4] the variegated history in the evolution of “axial” elements has resulted in a difficult-to-interpret literature of revisionist and deconstructionist “stereochemical taxonomy”. Spirocycles, biaryls, cyclophanes, metallocenes, and allenes have been at times ordained “axes” or “planes” only later to be defrocked as the “theologians” grappled with questions ranging from the role of conformation and connectivity under constraints of time scales and degrees of freedom, to the subtleties of descriptor choice such as *R/S* versus *P/M*. So much attention has been given to trying to find a concrete definition of the fundamental elements, that little has been said about molecules where multiple “axial” elements need to be confronted; complex issues of directionality leading to cyclostereoisomerism is left to the chemotalmudic scholars.^[5] This lack of serious theoretical underpinning is at the root of the recent confusion in the nomenclature of certain glycopep-

tide antibiotics.^[6–9] With the increasing prevalence of compounds containing stereogenic axes, notably in complex natural products, molecular switches^[10] and supramolecular constructs,^[11] an open discussion of the CIP system within the context of a complex molecule is warranted. We will use vancomycin^[6, 12] (**1**, Scheme 1) as a vehicle for discussing molecules with a broad spectrum of stereoelements, in particular multiple stereogenic axes. Consideration of the stereochemistry in this class of natural products motivated us to propose a concise and simple convention for describing stereogenic axes that we feel is an implicit extension of the CIP system^[3] and establishes a direct distinction between axial and central elements without recourse to additional descriptors.

Vancomycin and its relatives, the glycopeptide antibiotics, constitute a large and indispensable class of clinical antibiotics; they are the drugs of last resort for the treatment of antibiotic-resistant bacteria.^[6, 12] The glycopeptide antibiotics also possess a wealth of stereochemical elements exemplifying some of the most intriguing aspects of stereochemistry. Not only do they possess multiple stereogenic centers and axes, but within their structures one can identify the potential for the subtle and intricate stereochemical feature of directional cyclostereoisomerism,^[5, 13–16] an often overlooked and little discussed phenomenon.

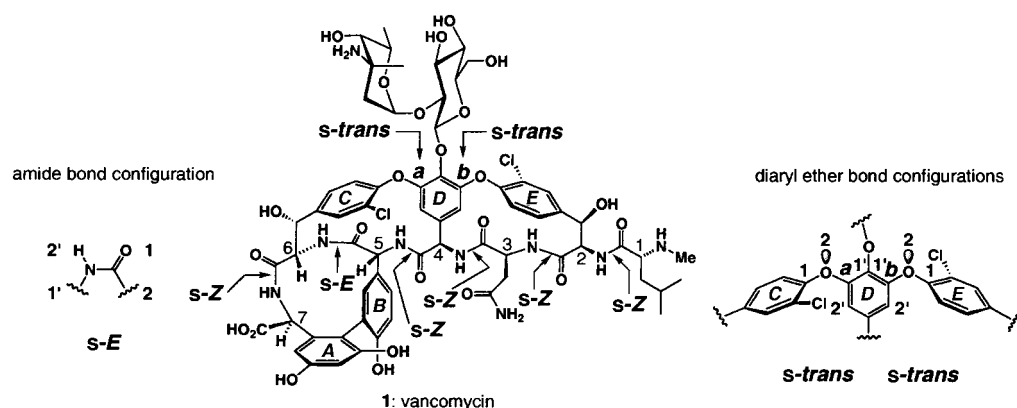
The glycopeptide antibiotics contain four principal structural domains (sugar, peptide, biaryl, and diaryl ether) and numerous stereochemical elements. The peptide domains of these molecules have between seven and nine stereogenic centers. Of the seven amino acids that make up the peptide domain of vancomycin (**1**), three possess the *S* configuration and four possess the *R* configuration (Scheme 1). Two of the amino acids present possess a second stereogenic center at their β -carbon atoms. The cyclopeptide cores of these molecules are adorned with varying numbers of sugar residues, an occurrence that significantly increases their number of stereogenic centers. If one considers only these centers, vancomycin (**1**) has 2¹⁷ (131 072) possible topographical configurations,^[17] a remarkable platform for stereochemical-based molecular diversity.^[18]

Vancomycin and the glycopeptide antibiotics can also exist, in principle, in two distinct types of *cis*–*trans* stereoisomers. Amide bonds can have either the *s-Z* or the *s-E* configuration. The majority of the amide bonds in the glycopeptide anti-

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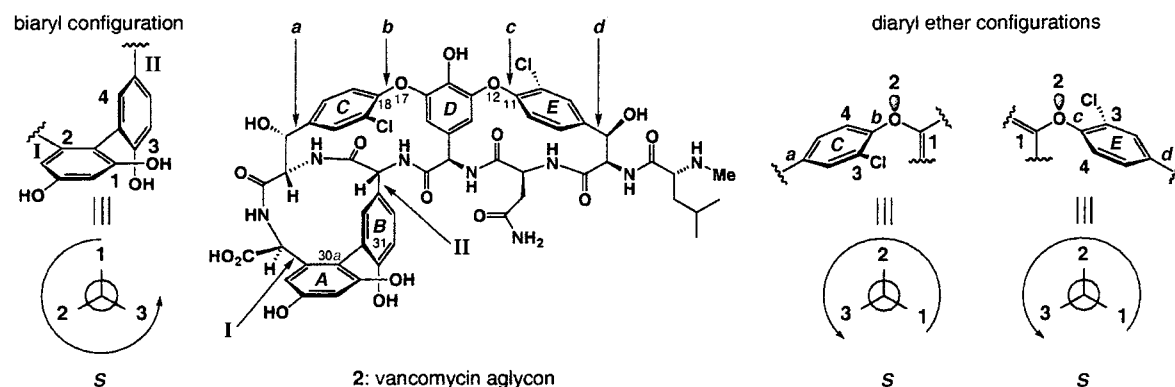
[**] We would like to thank Professor Dieter Hellwinkel for pointing out to us the stereochemical discrepancies in our review^[6] and elsewhere in the literature, and Kurt Mislow for stimulating and useful discussions.



Scheme 1. There are two types of *cis-trans* isomers in the glycopeptide antibiotics as exemplified by vancomycin (1). The amide bonds possess both the *s-Z* and *s-E* configurations as shown. The diaryl ether ring systems have two stereochemical elements *a* and *b*. These are constrained by the ring size in the *s-trans* configuration.

biotics are in the *s-Z* configuration. However, the amide bond connecting amino acids 5 and 6 is found in the *s-E* configuration (Scheme 1).^[19, 20] A second type of *cis-trans* isomer may manifest itself in the diaryl ether domain. Rigorously speaking, the bonds labeled *a* and *b* are stereochemical elements. These elements could potentially exist in either the *s-cis* or the *s-trans* configuration. The ring size, however, constrains both of these elements into the *s-trans* configuration (Scheme 1).

The biaryl and diaryl ether domains of the glycopeptide antibiotics possess no less than seven stereogenic axes, which are associated with the phenomenon of atropisomerism.^[21] One stereogenic axis is located in the biaryl ring system (*AB*, Scheme 2). Restricted rotation about the biaryl bond, as a result of constrictions imposed by the macrocycle's ring size and the substitution of the aromatic rings, gives rise to two possible isomers. All biogenic glycopeptide antibiotics possess the same configuration as seen in Scheme 2,^[6] although models of the biaryl ring system have been synthesized with both atropisomeric configurations.^[20] Two additional axes stem from the connection of the biaryl ring to the 12-membered macrocycle. These are correlated with the biaryl axis by the tight ring constraints, but are nonetheless stereochemically unique. The diaryl ether domains of the glycopeptide antibiotics (*C-O-D* and *D-O-E*, Scheme 2) can also display atropisomerism. Thus, as a consequence of the



Scheme 2. Atropisomers are generated from restricted rotation about three stereogenic axes in the vancomycin aglycon (2). The biaryl bond is one stereogenic axis as are the bonds labeled I and II. The biaryl bond in the shown atropisomer is in the *S* configuration. The bonds in both the diaryl ether ring systems labeled *a-d* are all stereogenic axes. The axes *b* and *c* are in the *S* configuration.

chlorine substituents on the aromatic rings and constraints imposed by the macrocycle's ring size, the bonds labeled *a-d* (Scheme 2) are stereogenic axes. Both of the diaryl ether ring systems in the vancomycin aglycon (2, Scheme 2) bear the same configurations.^[6] In fact, the diaryl ether ring systems in all of the naturally occurring glycopeptide antibiotics possess the same configurations. Synthetic intermediates of vancomycin with either atropisomeric configuration have, however,

been reported.^[7, 8, 22-25]

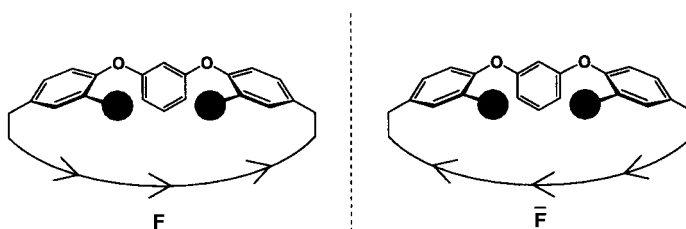
The identification and naming of this multitude of stereogenic axes presents a considerable nomenclature problem. The selection of an appropriate descriptor and identification of its location are not transparent operations because of historical inconsistencies in the CIP system. The classification of stereogenic units into centers, axes, and planes was introduced by Cahn, Ingold, and Prelog in their seminal treatise on stereochemistry in 1956.^[1] Since that initial description, stereogenic axes and planes have stimulated a great deal of discussion.^[2-4, 26] Stereogenic axes and planes were devised in the CIP system to describe systems that could not be adequately defined by stereogenic atoms alone.^[2, 27] The stereochemical descriptors *R* and *S* were prescribed in 1966 for the description of all stereogenic units. The prefixes *a* and *p* were introduced to distinguish stereogenic axes and stereogenic planes, thus *aR* and *aS* would define a stereogenic axis and *pR* and *pS* would be used to define a stereogenic plane.^[2] Hirschmann and Hanson simplified matters by showing that axes and planes could be resolved into a single element.^[4] The essence of their argument was stipulated by Prelog and Helmchen in 1982.^[3] Nonetheless, nomenclature for the stereogenic axis remained ill-applied in the community.^[28]

Cahn, Ingold, and Prelog introduced a further distinction among stereogenic axes^[2] in their discussion of configurational versus conformational stereoisomers.^[29] Configurational stereogenic axes were to be defined with the *aR* and *aS* descriptors, whereas conformational stereogenic axes were to be described by the *P* and *M* descriptors. Cahn, Ingold, and Prelog, however, loosened their conviction by stating that “both methods of specifying the chirality of (conformational stereogenic axes) would be regarded as available.”^[2] They also implied that a distinction between configurational and conformational stereogenic elements should not be a basis for stereochemical terminology. Recently, this view has been boldly reasserted by Helmchen.^[30] Surprisingly then, in the 1982 revision of the CIP system, stereogenic axes were considered conformational and as such it is prescribed that they should be defined by the helical descriptors *P* and *M*.^[3] Nonetheless, many substances, such as chiral biaryls and allenes, have remained defiantly unchanged by this vicissitude.

It is of little surprise then that many investigators are left somewhat confused by the vast array of choices provided by the CIP system in naming stereogenic axes. Our recommendation is to stick to the simplest naming scheme that will identify the location and configuration of each element. For that, *R* and *S* retain primacy and a locator is used to distinguish an axis from a center and specify the location in the molecule. Thus, (30*a*:31*S*) clearly identifies the location and sets the configuration of the biaryl axis.^[31–33] The use of the *P* and *M* descriptors is superfluous as a result of the ability of the *R* and *S* descriptors to adequately and unambiguously define these stereogenic elements. In fact, the use of *P* and *M*, which still require a locator, only confuses matters by introducing conformational versus configurational issues.

It is the opinion of the authors that the helical descriptors *P* and *M* be retained for systems in which *R* and *S* are inadequate in describing the stereochemical elements, such as with helical double-stranded DNA (the B form of DNA possesses the *P* configuration while the Z form possess the *M* configuration). This recommendation resonates well with the guiding principles Prelog and Helmchen^[3] outlined in their revision of the CIP system. That is that “... previously assigned descriptors should remain unchanged as far as possible ...,” and that there be “... self-restraint in introducing yet more to the already existing surfeit of new stereochemical terms ...”^[3]

Lastly, the family of glycopeptide antibiotics contains an element of directionality in their peptide backbones which can give rise to cyclostereoisomerism.^[5, 13–16] This type of isomerism is quite subtle and often overlooked. It was initially proposed^[13] and investigated^[14] by Prelog and co-workers and critically revised to be consistent with a proper symmetry analysis.^[5, 15, 16] Cyclostereoisomers are directional isomers;^[5, 15] that is, they rely on the directionality of the constituent chemical bonds (namely, a peptide bond could be -C(O)N(H)- or -N(H)C(O)-) to give rise to isomers. Examination of the diaryl ether macrocycles of the glycopeptide antibiotics shows that these structures exhibit many of the features necessary for cycloisomerism. The hypothetical glycopeptide antibiotic shown in Scheme 3 is used to illustrate



Scheme 3. This hypothetical glycopeptide antibiotic exhibits cyclostereoisomerism. The directionality of the peptide bonds differentiates one cyclostereoisomer from the other.

this phenomenon. The *meso*-like configuration of the atropisomers in the diaryl ether ring systems without the directional element of the peptide bonds would be invariant under reflection. The addition of the directional element arising from the peptide bonds, however, gives rise to cyclostereoisomers. This condition is maintained even if the peptide backbone is void of any stereocenters (for example, in an all-glycine backbone).^[34]

As masterpieces of molecular engineering by nature, the glycopeptide antibiotics contain a wealth of intriguing stereochemical elements. In this essay, we have attempted to delineate a variety of these stereochemical elements and to present a nomenclature that should facilitate communication among researchers in the field. In particular, we have proposed a convention for naming stereogenic axes. Following this convention the stereogenic axes in vancomycin (**1**) are named (11:12*S*, 17:18*S*, 30*a*:31*S*)-vancomycin (see Scheme 2 for numbering).^[33] In addition, we have shown that the glycopeptide antibiotics provide an interesting starting point for the exploration of cyclostereoisomerism and its potential impact on biologically active molecules.

Recent advances in chemistry, biology, and material science are requiring that the CIP system be applied to molecules that are currently beyond its scope. The CIP system has performed admirably thus far, but it is time to revisit its treatment of stereogenic axes and bring it up to date with recent scientific advances. While, we recommend adoption of our proposed convention, our primary motivation in writing this article was to initiate discourse that will lead to a clarification of the treatment of stereogenic axes by the CIP system.

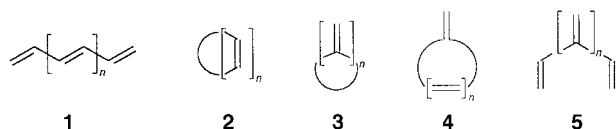
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- [17] One should note that vancomycin (**1**) and all other glycopeptide antibiotics are composed of both proteinogenic and nonproteinogenic amino acids as well as common and uncommon sugars, thus ²¹⁷ is a true measure of the molecular diversity possible from the 17 stereogenic centers.
- [18] *Combinatorial Chemistry and Molecular Diversity in Drug Discovery* (Eds.: M. Gordon, J. F. Kerwin, Jr.), Wiley, New York, **1998**.
- [19] It should be noted that the *cis*–*trans* configurations of the amide bonds in the glycopeptide antibiotics have been frequently misassigned.^[6, 20] The correct assignment is shown in Scheme 1.
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- [25] The configuration of the diaryl ether ring systems in the glycopeptide antibiotics have been frequently misassigned.^[6–8] The correct assignments are given here.
- [26] K. Mislow, J. Siegel, *J. Am. Chem. Soc.* **1984**, *106*, 3319–3328.
- [27] It is somewhat surprising that Cahn, Ingold, and Prelog prescribed factorization of structures into centers, axes, and planes. They stated in 1966 that a “chiral centre that is not the seat of an atom can be contemplated.”^[2] Following this train of thought, it is easy to eliminate the need for both stereogenic axes and planes, certainly within all the examples described by Cahn, Ingold, and Prelog.^[1, 2] All stereogenic elements can, thus, be viewed as stereogenic centers.^[4, 26]
- [28] It is noteworthy that even in Eliel’s stereochemical compendium^[9] it is difficult to find an unambiguous naming for an axial element as simple as a chiral allene.
- [29] “By configuration is meant the space-arrangement of a model representing a molecular state with neglect of the distinctions between varieties of that state which differ only as after relative rotations of groups directly bonded together, about internuclear lines of their intervening, formally single bonds; and by a conformational molecular state ... is meant a space-arrangement which signalises such a distinction, and identifies such a variety-state.”^[2]
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- [31] To correctly determine the absolute configuration of a stereogenic axis it is necessary to rank the substituents using the CIP sequence rules.^[32] First the atoms of the axis are ranked. The groups on the higher ranking side of the axis are given the ranks of 1 and 2, while the groups on the other side of the axis are then given the ranks of 3 and 4. If the atoms of the axis are of the same rank the overall highest priority group is ranked 1. Its geminal substituent is ranked 2. The groups on the other side of the axis are then ranked 3 and 4. These four groups, with the stereogenic axis as the center, are envisioned to form an elongated tetrahedron and can now be assigned as *R* or *S*, as is shown in Scheme 2.
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- [33] The complete numbering system for vancomycin (**1**) can be found in ref. [6]. In designating the stereogenic axes, each axis is defined by the atoms at the two ends of the structural unit defining the axis; the numbers defining the atoms are separated by a colon; and the stereochemical descriptor *R* or *S* follows.
- [34] While it is true that the two isomeric forms shown in Scheme 3 can be distinguished through appropriate numbering and assignment of stereochemical descriptors, this in no way precludes them from being cyclostereoisomers. In fact, any two cyclostereoisomers can be distinguished by appropriate numbering and assignment of stereochemical descriptors. Thus, at the simplest level the two isomers of *cis*-3,5-dimethylcaprolactam can be considered cyclostereoisomers.

Dendralenes: The Breakthrough

Henning Hopf*

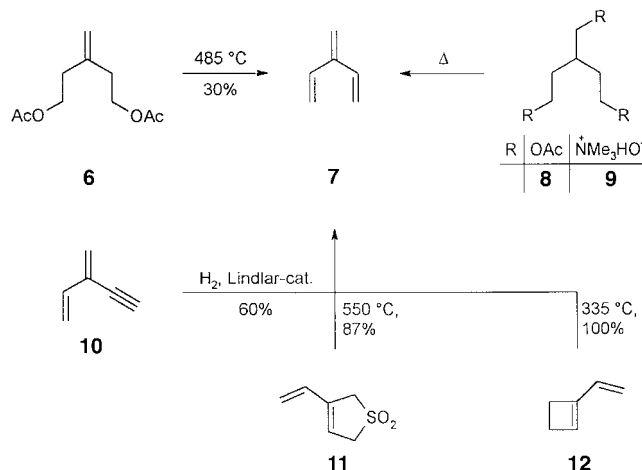
By connecting double and single bonds, formally five classes of hydrocarbons can be constructed which differ considerably from one another not only chemically and physically but also in terms of their practical significance:^[1] linear polyenes **1**; annulenes **2**, which consist exclusively of



endocyclic "double bonds"; radialenes **3**, polyolefins which are characterized by semicyclic double bonds; fulvenes **4**, hybrids consisting of endo- and semicyclic double bonds; and finally, dendralenes **5**,^[2] which are acyclic cross-conjugated polyenes.

Of these π systems, the first two are by far the most thoroughly investigated and also play the greatest practical role, be it in the form of vital molecules such as β -carotene or as key substances in organic syntheses, such as benzene. Of the remaining three substance classes, which are all cross-conjugated, fulvenes and their derivatives have been studied most extensively; however, in the last few years radialenes have gradually come out of the shadows.^[3, 4] Although von Auwers had obtained the first dendralene derivatives at the beginning of the twentieth century and this substance class was later studied by Staudinger, among others, who described them as "open fulvenes",^[2] there have been no in depth studies of the chemistry of the parent dendralene systems. The reason for this is simple: Except for compounds **5** with $n = 1$ ([3]dendralene **7**, Scheme 1) and $n = 2$ ([4]dendralene **15**, Scheme 2), higher vinylogues were not known until the recent investigations by Sherburn et al., details of which are given below.

A considerable number of processes have been described for the preparation of the two simplest dendralenes; however, most of them are rather means of formation than efficient preparative methods. As Scheme 1 shows for [3]dendralene **7**, thermal methods of preparation predominate (eliminations



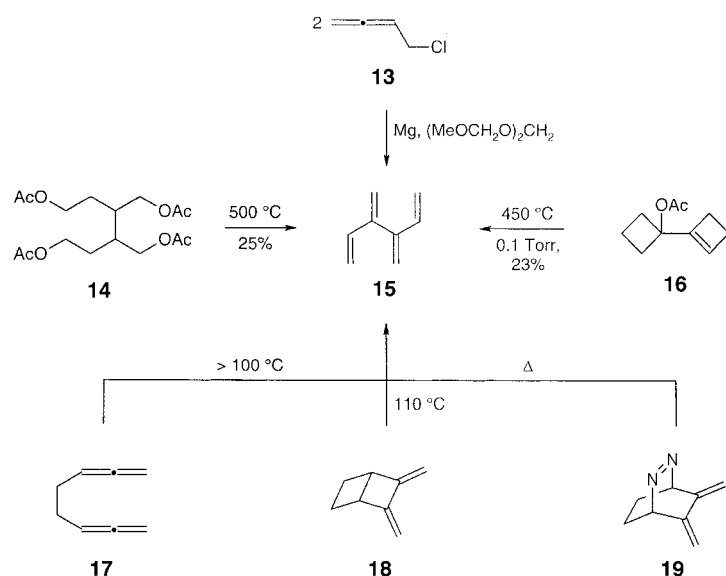
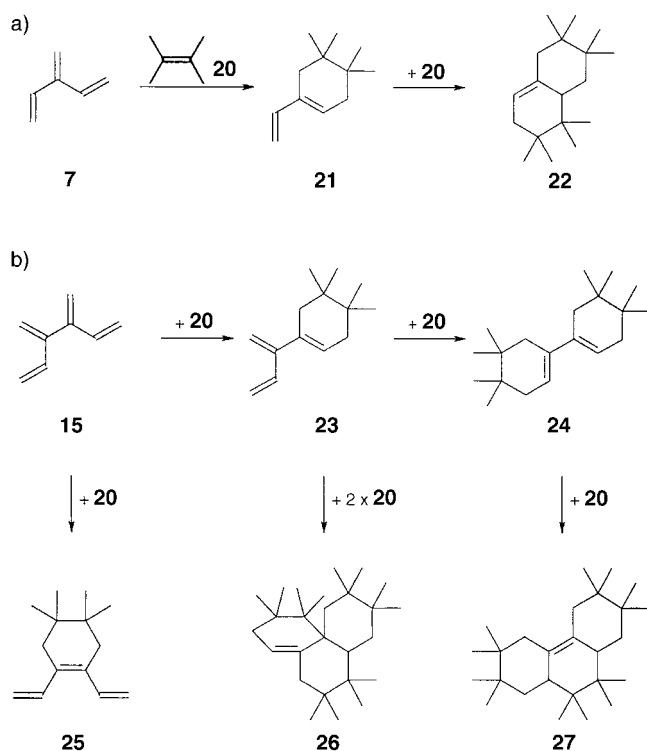
Scheme 1. Routes to [3]dendralene **7**.

and pericyclic processes); however, these methods do not always start from readily accessible precursors.^[5] The most effective—and therefore suitable for subsequent reaction chemistry—is the cheletropic decomposition of **11** carried out by Cadogan and Gosney et al.,^[6] although this sulfolene derivative first appears at the end of a reaction path with several steps. The situation was even more critical for [4]dendralene **15**,^[2, 7] especially since the thermal decomposition reactions represented in the lower half of Scheme 2 have all been carried out in the course of mechanistic studies.

Before the first general synthesis concept for the preparation of dendralenes is presented, it will be shown that these π systems, neglected until now, are interesting not only preparatively but also from a structural point of view. The application of dendralenes in Diels–Alder additions holds particular promise in synthetic chemistry. This is outlined in more detail in Scheme 3 for the two simplest dendralenes. The [2+4] cycloaddition of **7** with a dienophile **20**, not only leads to the expected 1:1 adduct **21** but also generates a conjugated diene system which is available for a second addition with **20** to give **22** (Scheme 3 a). In principle, dienophiles containing a triple bond and heteroorganic addends are also suitable as dienophile components.

Tsuge and co-workers—building on work by Bailey and Blomquist^[5]—have already made extensive use of the preparative potential of these types of diene transmissive Diels–Alder additions^[8]. Clearly, the dienophile does not have to be identical in the two stages of the reaction, which increases the

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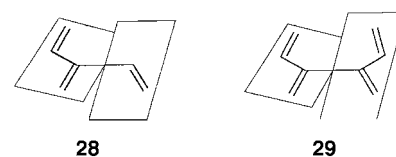
Scheme 2. Routes to [4]dendralene **15**.Scheme 3. Diene-transmissive Diels-Alder additions with **7** and **15**.

preparative potential of these double cycloadditions considerably. The adducts of type **22** can be further processed in various ways, for example by dehydrogenation to give 1,2,6,7-tetrasubstituted naphthalene derivatives. Consecutive reactions of this type with their excellent atom economy are of considerable interest particularly in view of the current efforts to increase the efficiency of organic transformations.

As expected, the possibilities for [4]dendralene **15**, which until now has only been used occasionally in diene-transmissive additions,^[7c] to participate in [2+4] cycloadditions are much greater (Scheme 3b). Two possibilities arise for the first addition, depending on whether **20** adds to a terminal diene

unit (formation of **23**) or to the central diene unit (formation of **25**). For **23**, two further alternatives are offered which could either lead via **24** to the 3:1 adduct **27** or—by consecutive additions of two equivalent dienophiles—to the tris-adduct **26** (notice the formation of a quaternary carbon atom in **26**). Depending on the type of dienophile, the adducts **27** could also be used again for aromatization experiments. New types of products are also expected in many other reactions of dendralenes (photochemistry, metal complexation, ionic additions).

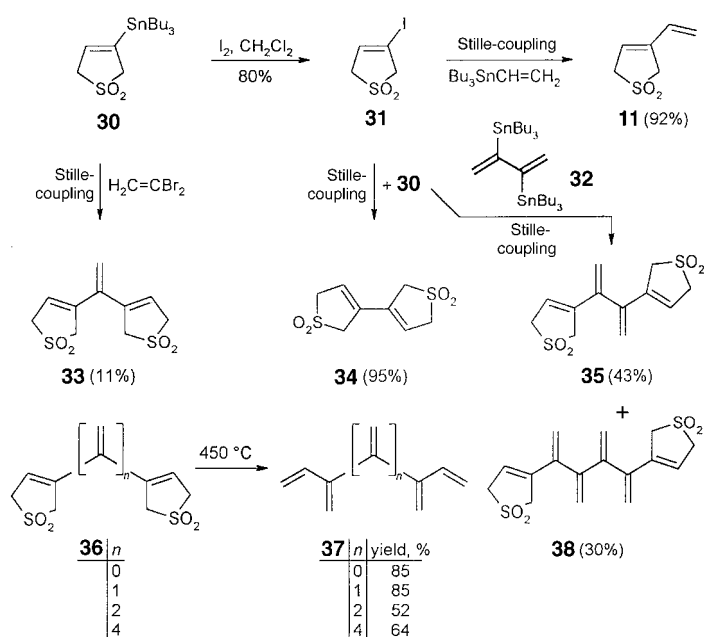
As far as the structure of dendralenes is concerned the early work concentrated on the analysis of UV spectra—not surprising if one considers that the cross-conjugation motif occurs in many dyes (triphenylmethane dyes, indigo etc.). The electronic spectra show, for instance, that the dendralenes cannot exist in coplanar form. Their absorption maxima lie in the same region as in simple 1,3-dienes; they are not shifted to longer wavelengths as one would expect for an extended π -electron system. This is confirmed by detailed structural investigations accompanied by various calculation methods. According to electron diffraction measurements, **7** has the *anti*, *skew* conformation **28** with a dihedral angle of 40° between the planes of the *anti*-butadiene fragment and the remaining vinyl group.^[9] In **15** this dihedral angle is 72° and again the *anti*-butadiene halves are practically planar (see structure **29**).^[10]



The unsatisfactory situation that promising substance class could not be developed further has recently been rectified by the groups of Fielder, Rowan, and Sherburn in Australia/New Zealand who have achieved a general route to dendralenes.^[11] In planning the corresponding sequence, the well known instability and tendency to polymerize of dendralenes **7** and **15** were taken into consideration from the very beginning, in that a synthetic route was designed in which the dendralene π system is not released until the very end. In particular the butadiene fragment was transported in capped form as a sulfolene ring to the end of the synthesis, as Cadogan and Gosney et al.^[6] had done for the simplest dendralene **7**.

As Scheme 4 shows, the synthesis developed by Sherburn et al. begins with the vinyl stannane **30**, which is initially converted by iodolysis to the vinyl iodide **31**. The actual “construction” then followed through Stille cross-couplings; the mild reaction conditions used prevented the premature release of the sulfur dioxide from the masked dendralene intermediates. The sulfolenes **11**, **33**, and **34** were obtained readily in the presence of $[\text{PdCl}_2(\text{CH}_3\text{CN})_2]$ in DMF under argon at temperatures up to 40 °C. The coupling of **31** with the bis-stannane **32**, not only gave the bis-sulfolene **35**, but also the [8]dendralene precursor **38**.

The masked dendralenes **36** are crystalline compounds, stable at room temperature from which, as hoped, the



Scheme 4. General dendralene synthesis according to Sherburn et al.

hydrocarbons **37** are released on demand in good yields by high-temperature pyrolysis. As no solvent is required in these cheletropic reactions, the workup is clearly made easier. The dendralenes **37** obtained, up to [8]dendralene ($n=6$), have been completely characterized by the usual spectroscopic and analytical methods and can, although they have a tendency to polymerize, be manipulated—the deciding prerequisite for the study of their reactivity.

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The First Cadmium-Specific Enzyme

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Is the Biochemistry of Cadmium More Similar to That of Zinc or Mercury?

From a biological point of view, group 12 of the periodic table is remarkable. Its lightest element, zinc, occurs as an essential constituent in numerous proteins. However, the situation is entirely different for the heaviest group homologue, mercury. This is considered one of the most toxic nonradioactive elements. Also in the case of cadmium, which is the middle element of the group, toxicity and carcinogenicity have been nearly exclusively in the foreground so far. Positive biological effects, for example, on the growth of a

fungus species,^[1] have been described only sporadically and remain biochemically unexplained. The recently published discovery of the first cadmium enzyme can therefore rank as a landmark in the biological chemistry of cadmium.^[2]

Cadmium quite clearly differs chemically from mercury. This is true for many aspects of the toxicity as well. For example, the alkyl species MR_2 and RM^+ are only slowly degraded in the case of mercury and therefore show a characteristic symptomatology of poisoning,^[3] while in the case of cadmium the species are not of any special toxicological importance because of their fast hydrolysis to Cd^{2+} . On the other hand it has been known for a long time that, in its compounds, cadmium often resembles zinc. Against this background it should thus not be too surprising that cadmium can also have a defined function in organisms. However, nothing of that became visible in the biological career of this element during the first 140 years after its discovery (Table 1).

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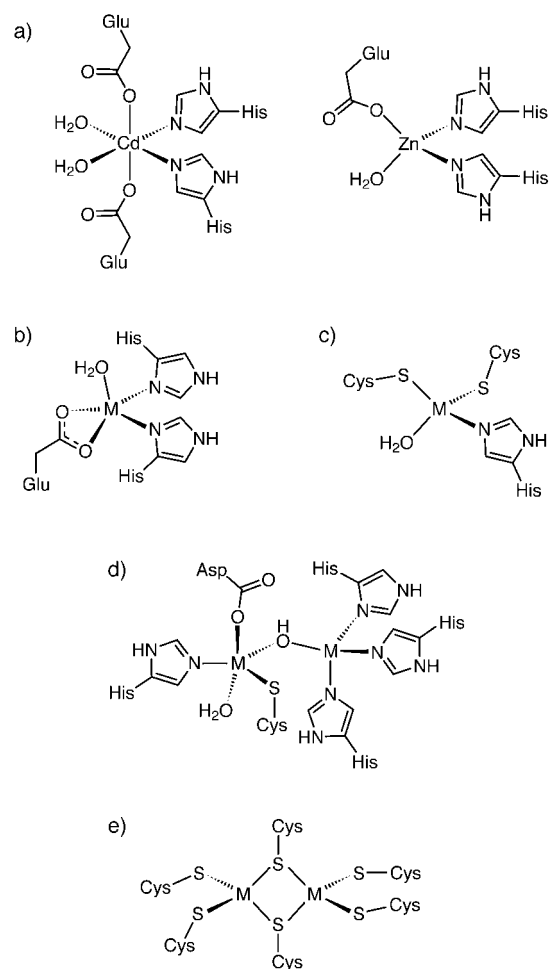
Table 1. A brief chronicle of the biological chemistry of cadmium.

1858	40 years after the discovery of the element, the first cases of cadmium poisoning in humans are reported
1946	Beginning of the systematic study of the itai-itai disease in Japan; about 20 years later cadmium poisoning is suspected for the first time as being a coinducing factor
1961	Results of animal experiments give the first indications of the carcinogenic potential of cadmium; in 1993 the International Agency for Research on Cancer classifies cadmium as a human carcinogen
	In the zinc enzyme carboxypeptidase A, Zn^{2+} can be substituted by Cd^{2+} ; the Cd-substituted enzyme continues to show esterase activity, but the peptidase activity is largely lost
1981	It is reported that cadmium has a growth-promoting effect on a mushroom species, but it cannot compensate for zinc deficiency
1985	Crystallographic studies show that the structure of the active site of an alcohol dehydrogenase changes only slightly when the native Zn^{2+} is substituted by Cd^{2+} ; nevertheless the enzymatic activity is greatly reduced
1989	The first cadmium-activated enzyme, phytochelatin synthase, is described
1990	A possible relation between the carcinogenicity of cadmium and the experimentally established substitution of Zn^{2+} by Cd^{2+} in gene-regulating “zinc-finger” proteins is discussed
	Under conditions where zinc is scarce, the marine diatom <i>Thalassiosira weissflogii</i> utilizes cadmium as an alternative bioelement
1994	It is assumed that <i>T. weissflogii</i> substitutes deficient zinc by cadmium in the zinc enzyme carbonic anhydrase
2000	The substitution hypothesis turns out to be incorrect; <i>T. weissflogii</i> synthesizes a novel cadmium-specific carbonic anhydrase—the first cadmium enzyme is discovered

Cadmium-Substituted Zinc Proteins

The way for cadmium as a “bioelement” was essentially paved by investigations on zinc proteins. In 1961 Coleman and Vallee showed that the native metal ion can be removed from the zinc enzyme carboxypeptidase A by use of chelating agents and that Cd^{2+} ions can then be introduced into the apoenzyme.^[4] Many other cadmium-substituted zinc proteins followed. In contrast to the situation with the spectroscopically “dead” zinc, it was now possible to utilize the potential of ^{113}Cd NMR and ^{111}Cd PAC spectroscopy (PAC = perturbed angular correlation of γ -rays) in order to study the structures of the metal centers.

The enzymatic activity of the cadmium forms, however, is mostly lower than that of the zinc enzymes and sometimes no longer present at all. This is caused by the different ionic radii of Cd^{2+} and Zn^{2+} . The markedly larger Cd^{2+} ion prefers higher coordination numbers and is a weaker Lewis acid. In the extreme case of thermolysin, the metal is six-coordinate in the cadmium form $[\text{Cd}(\text{N} \cdot \text{His})_2(\text{O}_2\text{C} \cdot \text{Glu})_2(\text{OH}_2)_2]$ and four- or five-coordinate in the zinc form $[\text{Zn}(\text{N} \cdot \text{His})_2(\text{O}_2\text{C} \cdot \text{Glu})(\text{OH}_2)]$ (Scheme 1 a).^[5] This difference obviously accounts for the fact that cadmium-substituted thermolysin is totally enzymatically inactive. With other zinc enzymes, such as carboxypeptidase A,^[6] horse liver alcohol dehydrogenase,^[7] and metallo- β -lactamase,^[8] the metal environments remain intact in the cadmium forms (Scheme 1 b–d). Nevertheless, the enzyme activities here are significantly reduced as well, probably because the less Lewis acidic Cd^{2+} ion has a weaker

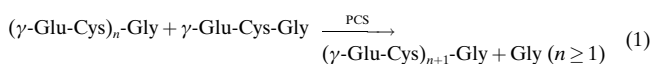


Scheme 1. Schematic representation of the metal coordination in cadmium-substituted zinc proteins and in the corresponding native forms ($\text{M} = \text{Cd}, \text{Zn}$). a) The catalytic center of thermolysin; in the Zn form the carboxylate group can also be η^2 -coordinating—this is probably dependent on the pH value. b) Carboxypeptidase A. c) The catalytic center of alcohol dehydrogenase. d) Metallo- β -lactamase. e) GAL4.

polarizing effect on its environment. This is the reason why, among other things, coordinated substrates are less activated and the pK_a values of coordinated water molecules are not as strongly decreased. Also, it is noteworthy that in gene-regulating proteins cadmium ions can substitute for the structure-stabilizing zinc ions without inducing drastic changes. For example, in the transcription factor GAL4 the dinuclear metal center continues to exist (Scheme 1 e).^[9] As gene-regulating proteins interact directly with DNA, a causal relation to the carcinogenicity of cadmium is conceivable.^[10]

Phytochelatin Synthase, a Cadmium-Activated Enzyme

Phytochelatin synthase is a short peptide of the composition $(\gamma\text{-Glu-Cys})_n\text{-Gly}$ ($n = 2-11$), which in plants serve, inter alia, for cadmium detoxification. They are biosynthesized from the tripeptide glutathione ($\gamma\text{-Glu-Cys-Gly}$) by the enzyme γ -glutamylcysteine dipeptidyl transpeptidase (phytochelatin synthase, PCS) [Eq. (1)].



Interestingly, the PCS molecules are initially inactive and are activated only by cadmium ions that have entered the plant cell.^[11] The subsequently synthesized phytochelatins form stable Cd^{2+} complexes,^[12] so that after some time the enzyme reaction breaks down for lack of cadmium. Thus PCS is self-regulating. The molecular mechanism of the activation is still unclear. It seems uncertain whether the cadmium is located in the catalytic center of the enzyme because, although Cd^{2+} is the most effective activator, various other metal ions can, in some cases considerably, activate PCS too.^[11, 13]

Cadmium Carbonic Anhydrase, the First Cadmium Enzyme

The starting point for the discovery of the cadmium carbonic anhydrase was the observation that the concentration of cadmium in sea water follows that of nutrients such as phosphate. That is, dissolved cadmium in water layers near the surface is often strongly depleted, obviously because cadmium is taken up by the phytoplankton. Zinc behaves completely analogously, and thus its availability is a growth-limiting factor for many marine microorganisms. The assumption seemed obvious that these organisms possibly utilize cadmium as a substitute for zinc. Price and Morel could indeed demonstrate on artificially zinc-limited cell cultures of the marine diatom *Thalassiosira weissflogii* that the drastic growth limitations which are caused by zinc deficiency can be largely compensated by addition of Cd^{2+} .^[14] However, when zinc is sufficiently available, cadmium does not act in a growth-promoting manner.

Soon a connection between these observations and the carbonic anhydrase activity was discovered.^[15] The zinc-containing carbonic anhydrases catalyze the hydration of CO_2 highly efficiently [Eq. (2)]. They play a key role, for example, in the photosynthetic CO_2 fixation in many photoautotrophic plants.^[16] Cadmium-substituted zinc carbonic anhydrases can exhibit significant enzymatic activity, although only in the alkaline pH region. It therefore seemed plausible to attribute the positive effect of cadmium in *T. weissflogii*, at least partly, to metal substitution in the zinc carbonic anhydrase (TWCA1). On the basis of more recent findings this hypothesis was, however, dismissed. Instead, Lane and Morel arrived at the surprising result that under conditions where zinc is scarce *T. weissflogii* can synthesize a special cadmium carbonic anhydrase (Cd-CA).^[2] This marks the discovery of the first defined biological function of cadmium. As zinc limitation generally occurs in the natural habitat of *T. weissflogii* (see above), cadmium must be regarded as an essential element for this organism.



Cd-CA is definitely not a cadmium-substituted TWCA1. The authors were able to give several proofs for this including, among other things, the different molar masses (Cd-CA: 43 kDa, TWCA1: 27 kDa). The function of Cd^{2+} as part of the catalytic center of the Cd-CA can hardly be doubted because

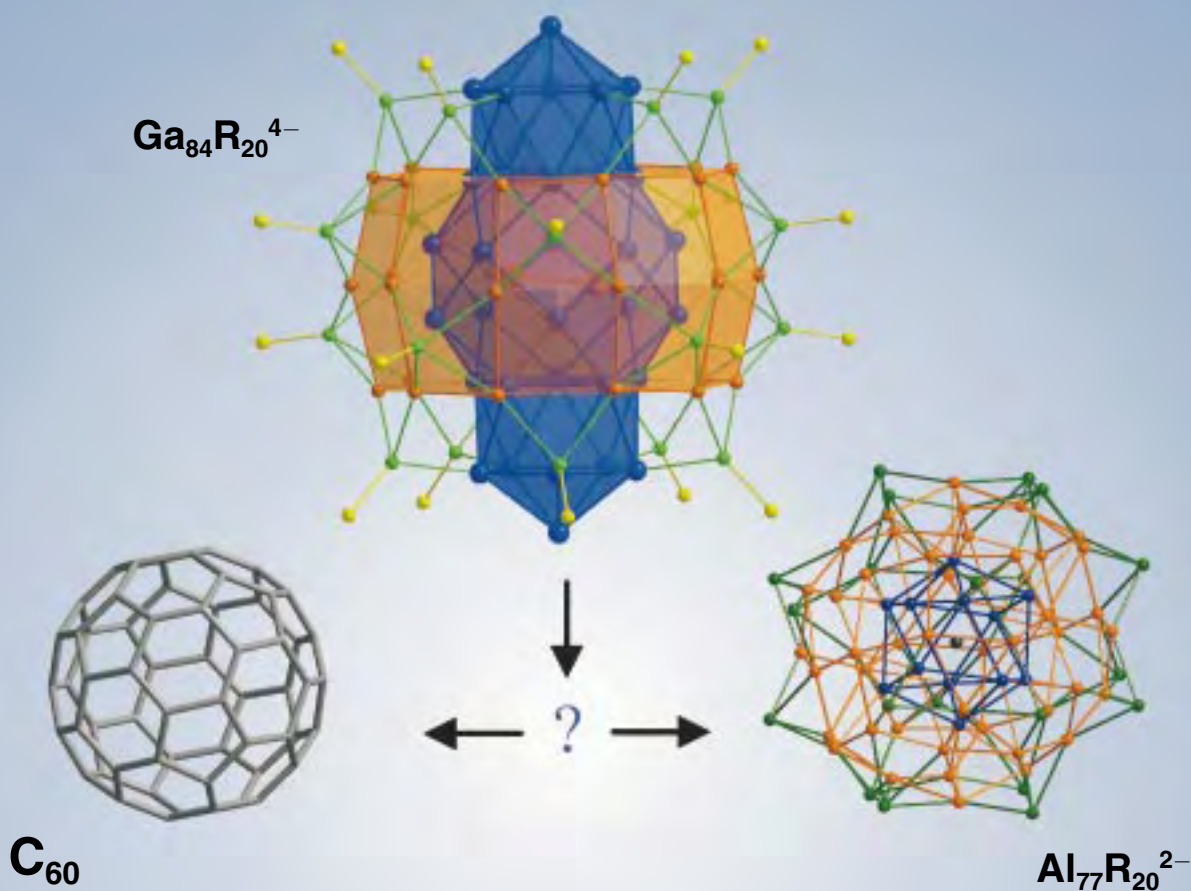
of the analogy with the zinc carbonic anhydrases. As soon as sufficient protein material is available, the full characterization will commence. One may be especially curious about the three-dimensional structure and particularly about the coordination of the cadmium. Recently, even the zinc carbonic anhydrases have offered surprises with respect to metal coordination: instead of the "classic" $\{\text{Zn}(\text{N} \cdot \text{His})_3(\text{OH}_2)\}$ center seen in the α - and γ -carbonic anhydrases, $\{\text{Zn}(\text{N} \cdot \text{His})(\text{S} \cdot \text{Cys})_2\text{L}\}$ centers ($\text{L} = \text{OH}_2$ or $\text{O}_2\text{C} \cdot \text{Asp}$) were discovered in β -carbonic anhydrases of plants.^[17]

In contrast to cadmium carbonic anhydrase, into whom investigation has only recently begun, the characterization of phytochelatin synthase has already proceeded a step further. At virtually the same time, three research groups reported on the first identification of PCS genes and the amino acid sequences belonging to them.^[18] Thus the goal of elucidating the mechanism of the activation by Cd^{2+} ions has moved a good deal closer. Not least by the new role of cadmium as a bioelement are the coordination chemists challenged to contribute to the understanding of the catalytic and structure-directing properties of Cd^{2+} ions in enzymes.

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The surprising geometry of a $\text{Ga}_{84}\text{R}_{20}^{4-}$ cluster ($\text{R} = \text{N}(\text{SiMe}_3)_2$) ...

- 64 “naked” Ga atoms, free of ligands, representing a new world record in the area of cluster research
- a Ga_2 unit in the center surrounded by a cigar-shaped Ga_{32} skeleton, with a central Ga-Ga separation close to that of the shortest known Ga-Ga bonds (“triple bond”)



... points to bonding properties,

which are intermediate between the class of **polyhedral clusters** with covalent bonds, the most prominent representatives being the fullerenes, and the typical **metalloid clusters**, such as the Pd_{145} and the $\text{Al}_{77}\text{R}_{20}^{2-}$ clusters.

Synthesis and Structure of a $\text{Ga}_{84}\text{R}_{20}^{4-}$ Cluster— A Link between Metalloid Clusters and Fullerenes?*

Andreas Schnepf und Hansgeorg Schnöckel*

*Dedicated to Professor Anthony J. Downs
on the occasion of his 65th birthday*

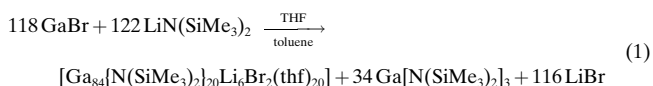
Metalloid clusters,^[1, 8] that is molecular metal clusters in which the number of direct metal–metal contacts exceeds that of the metal–ligand bonds, have been intensively studied worldwide for many years because of the potential of clusters of this type, for example, in the area of molecular electronics.^[2] The most prominent and most widely used species of this type is the Au_{55} cluster,^[2] although for this and for similar species, and in some cases larger Pd and Pt clusters, only structural information based on modern microscopic techniques is available.^[2] The largest metalloid precious metal cluster, characterized by diffraction, contains 59 Pd atoms,^[3] of which only 11 are “naked”, that is do not form ligand interactions. Thus, the structural elucidation of an Al_{77} cluster with 57 “naked” Al atoms by our group three years ago was surprising and shows the progress in the syntheses of these cluster compounds with regard to earlier processes.^[4] To understand the formation of this Al_{77} cluster, which can be interpreted as an intermediate on the pathway from metastable Al^{I} compounds prepared cryochemically^[5] to Al metal and to AlR_3 , we have tried to trap further intermediates on the pathway to the Al_{77} cluster under very mild reaction conditions over the last few years. With the same ligand, $\text{N}(\text{SiMe}_3)_2$, the number of Al atoms per cluster could be changed and compounds which contain 7,^[1] 12,^[6] 14,^[7] and finally 77 Al atoms could be obtained by varying the reaction temperature alone. In each of these clusters structural elements are present which are characteristic for aluminum as a typical metal, that is these clusters are in fact similar to metals, thus metalloid.^[1, 8]

Parallel to these experiments we started to produce analogous Ga clusters, since, owing to the variety of the solid-state modifications of gallium—exhibiting in some cases covalently bonded units,^[9] which are reminiscent of bonding modes displayed by boron—other structures and bonding situations are expected than those found in Al clusters.

Following our successful synthesis of a Ga_{19} ^[8] and a Ga_{22} cluster^[10] and the recent description of a Ga_{22} ^[11] and a Ga_{26} cluster,^[12] we report herein on a Ga_{84} cluster with 64 “naked” Ga atoms. This surpasses the Al_{77} cluster as the largest structurally characterized metalloid cluster in the entire field of metal atom clusters and displays a totally unexpected

structure in comparison to the Al_{77} cluster despite the same number and type of ligands.

The reaction of a metastable GaBr solution in toluene/THF (4/1), which was obtained by the cocondensation of the GaBr molecules—generated at about 1000 °C—in a toluene/THF solvent mixture,^[5] with a solution of $\text{LiN}(\text{SiMe}_3)_2$ gives black, metallic, shiny crystals of the composition $[\text{Ga}_{84}\{\text{N}(\text{SiMe}_3)_2\}_{20}]^{4-}$ (**1a**) after warming to 55 °C. The reaction proceeded according to Equation (1).



Only the listed products were generated and no elemental gallium was formed. The quality and size of the crystals (up to $1.5 \times 1.5 \times 0.5$ mm), which were thermally stable up to about 400 °C, allow a precise determination of the structure and open the way to studies of the physical properties (in progress). In the crystal structures the anionic Ga_{84} units $[\text{Ga}_{84}\{\text{N}(\text{SiMe}_3)_2\}_{20}]^{4-}$ (**1a**) (Figure 1) adopt a slightly distorted, cubic closest packing, in which the tetrahedral holes are completely occupied by $[\text{Li}(\text{thf})_4]^+$ ions and the octahedral holes with the dication $[(\text{thf})_3\text{LiBrLi}(\text{thf})_3]_2^{2+}$.

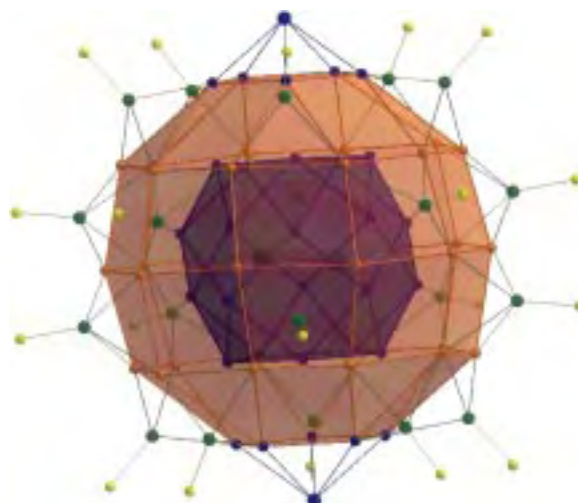


Figure 1. Molecular structure of $[\text{Ga}_{84}\{\text{N}(\text{SiMe}_3)_2\}_{20}]^{4-}$ (**1a**) in shell representation (without SiMe_3 groups).

Compound **1a** contains 84 Ga atoms, whereas in the corresponding Al cluster only 77 Al atoms are present in the analogous ligand shell of 20 $\text{N}(\text{SiMe}_3)_2$ groups. This finding appears plausible, as Ga–Ga bonds, for example in $\text{R}_2\text{M}–\text{MR}_2$ ($\text{M} = \text{Al}, \text{Ga}$; $\text{R} = \text{CH}(\text{SiMe}_3)_2$), are about 4.5 % shorter than Al–Al bonds.^[13] In the shell-like representation of **1a** (Figure 1), which was chosen analogously to that of the Al_{77} cluster, Ga–Ga distances have to be taken into account up to 368 pm (sum of the van der Waals radii 380 pm), that is, in this representation, a similarity to the Al_{77} cluster is only feigned. The difference between the Al_{77} cluster and **1a** becomes particularly clear on comparison of the coordination numbers: Whereas the coordination numbers for the Al_{77} cluster decrease from the center outwards from 12 through

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8 to 6, a small coordination number of only 4 has been noted for the inner shell of the Ga_{84} cluster, which increases to 8 in the next shell and subsequently decreases again to 4 further out. A different view of the bonding characteristics of the Ga_{84} cluster that focuses on the geometry of the 64 “naked” Ga atoms (Figure 2) appears better than this shell-like representation.

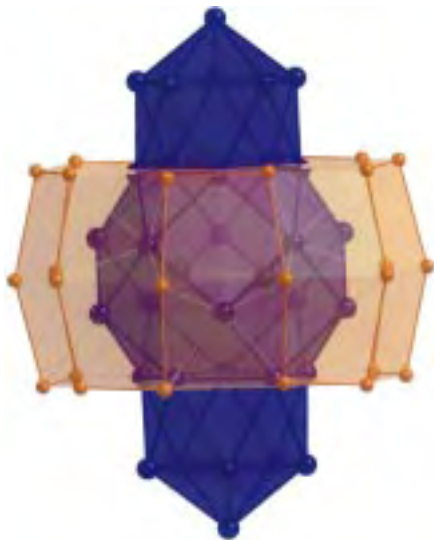


Figure 2. Polyhedral representation of the 64 gallium atoms not bound to one ligand. Ga–Ga distances (min./mean/max.) in the tube-shaped Ga_{32} unit: 262.8(2)/274.3/288.7(2) Å.

Notably, the Ga–Ga bond in the central Ga_2 group ($d(\text{Ga–Ga}) = 235$ pm) is as short as that of the so-called triple bond^[14] and the (blue) tube- or football-like Ga_{32} unit in which the mean Ga–Ga distance is only 278 pm. Here the Ga_{20} unit from Figure 1 is supplemented with two icosahedral Ga_6 caps, which according to the schematic shell model in Figure 1 should be assigned to the orange-colored shell. However, due to the significantly shorter distances to the Ga_{20} group, these Ga_6 caps are better assigned to the blue unit in Figure 1. The resulting Ga_{32} unit is surrounded by a further 30 “naked” Ga atoms, which wind around the Ga_{32} group with Ga–Ga distances in the following sequence: 273 pm (horizontally), 293 pm (vertically), 293 pm (vertically) and so on. These 30 Ga atoms form three planar Ga_{10} rings with in some cases very weak Ga–Ga bonds. This arrangement of naked Ga atoms is unique in the field of molecular compounds.

In contrast, in the solid-state structures of elemental gallium the structure of α -Ga with the unusual Ga_2 -dumbbell ($d(\text{Ga–Ga}) = 245$ pm) and the structure of δ -Ga with strongly distorted icosahedral Ga_{12} units (275–289 pm) show structural relationships with **1a**. As each of the coordination numbers in **1a** is lower than in the above-mentioned Ga element modifications (if only the bond lengths up to 289 pm are taken into account), the bonding in **1a** must be significantly more covalent. This consideration shows that **1a** has a topology in the environment of the Ga_{32} units that is similar to the more covalent bonding in the boranes or in the element structure of boron, and can partly be considered to be on the path to fullerenes.^[15] This somewhat bold relationship is based

on the fact that the Ga_{32} unit is a hollow body (apart from the central Ga_2 dumbbell) that only displays short distances of 276 pm (mean) to the three external Ga_{10} rings. This picture of a predominantly covalent partial structure of the Ga_{32} group is supported by the Ga_2 unit with an especially short Ga–Ga distance of 235 pm situated in the center of the Ga_{84} cluster, as endohedral species of fullerenes with, for example, Sc_2 ^[16] and even larger units (e.g. Sc_3N ^[17]) have also been synthesized very recently. In contrast to the fullerenes, **1a** represents to our knowledge a unique situation in the entire field of molecular species: An M_2 “molecule” is situated in a cage of 20 (or 32) atoms of the same metal. In contrast, a Sc_2 “molecule” in a C_{84} cage of nonmetal atoms is found in the above-mentioned endohedral fullerenes. There are numerous structural features of **1a** which point towards analogies with both the fullerenes and with the Al_{77} cluster, such that with respect to its structure, **1a** lies between both extremes. In accord with this classification of the bonding in the Ga_{84} cluster being between that in the Al_{77} cluster and that in the fullerenes, in the following a distinction should be made to the metalloid precious metal clusters.

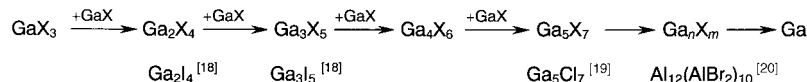
Both the experimental findings, based on microscopic methods, as well as theoretical considerations for these metalloid cluster groups generally lead to the result that the geometry of the metal atoms represents a section of the crystalline metal.

In contrast, our results for the shell-like Al_{77} cluster show that this view should be evaluated very critically. Evidently, the ligands and their bonding to the outer metal atoms play a decisive role in the formation of the cluster. In the case of the Al_{77} cluster, the coordination number 12 expected for the close packing is only found for the central Al atom; here also the ideal anticuboctahedral arrangement is not realized. The coordination numbers and the bond lengths decrease on moving to the outer shells, that is the bonding characteristics become more “molecular”. This view of metalloid, ligand-protected clusters is also supported by our results for **1a**: In the center of the cluster, the coordination numbers and building blocks are typical, for example, for α - and δ -gallium (dumbbell, icosahedra), whereas the outer-lying Ga–Ga bonds are more “molecular”, that is have distances similar to those in R_2GaGaR_2 or Ga_4R_4 units.

Furthermore, the formation of crystalline compounds for the Al_{77} and for the Ga_{84} clusters contradicts the tendency of the precious metal cluster compounds not to crystallize. This difference is plausible since here the stabilizing ligand shell is bound rigidly by 2e-2c bonds (AlN or GaN) to particular metal atoms. In contrast, transition metal clusters show a more flexible ligand shell through σ -donor and π -acceptor bonds (e.g. CO , PR_3 and SR_2) with in some cases bridging properties, which leads to stationary equilibria, in which many species that differ only slightly in terms of energy probably exist. Consequently, a high enough concentration of a distinct species, which is necessary for the formation of crystalline samples, is only obtained rarely.

The mechanism of formation of the Al and Ga clusters is also probably completely different. The principle of disproportionation is decisive; for reactive species such as MX ($\text{M} = \text{Al, Ga}$; $\text{X} = \text{halogen or organic substituent}$) it proceeds so

slowly at low temperatures that intermediates can be trapped before the thermodynamically stable bulk metal and the M^{III} species (e.g. $3MX \rightarrow 2M_{solid} + MX_3$) are finally formed. Through gradual insertion of MX units (excess) and elimination of MX_3 (or M_2X_4), cluster growth occurs (Scheme 1) which can be influenced by the choice of temperature, donor, halide, and the organic group.



Scheme 1. Growth of Ga_nX_m clusters (X = halogen) by insertion of GaX and elimination of GaX_3 or Ga_2X_4 units.

Thus, in the same chemical environment an Al_7 , Al_{12} , Al_{14} , or Al_{77} cluster can be obtained simply by variation of the temperature alone. The last step, the formation of the metal, only occurs if a critical cluster size is reached (e.g., by warming the solution to 100 °C) in the reducing atmosphere (MX excess); that is, a giant cluster is produced whose metal core is largely equivalent to the bulk material and which can disproportionate into metal and M^{III} species without large changes in the bonding.^[21]

The results presented here on a Ga_{84} cluster show that such disproportionations of reactive species also lead to success in systems that are outside the regime of typical metals and consequently lead to unusual cluster structures with predominantly covalently bonded units. Thus gentle disproportionation appears to be a successful synthesis concept for a diverse range of cluster compounds. For such compounds, for example, the analogous fullerenes,^[22] special properties, for example, with regard to the electrical conductivity are expected. In this respect, interesting effects can be expected already from the arrangement of the Ga_{84} units in the crystal (Figure 3); the Ga_{84} clusters are each separated by only two

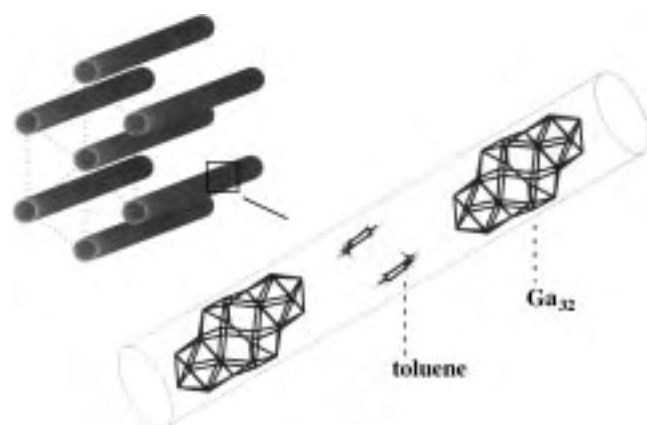


Figure 3. Arrangement of the Ga_{84} cluster in the crystal. For clarity only the Ga_{32} subunits are presented.

toluene molecules that are located over the “naked” apex atoms, leading to the formation of “tubes” of Ga_{84} clusters. Seen from the front (Figure 3), these “tubes” form a distorted hexagonal arrangement of pipes, which are separated from one another by the ligand shell. Now that we are in the position to synthesize sufficient amounts of **1** in crystalline

form, we have started conductivity measurements which are problematic due to the sensitivity of the crystals. If, as hoped, we find special physical properties of **1** (e.g. superconductivity as in the fullerenes), the interest in the Ga_{84} cluster in the interdisciplinary fields of chemistry, physics, and material sciences should increase rapidly and stimulate further efforts in the synthesis of these metalloid clusters.

Experimental Section

$LiN(SiMe_3)_2$ (1.8 g, 10 mmol) was added to toluene (30 mL) and cooled to -78°C . A GaBr solution (27 mL, 8.3 mmol of a 0.3 M solution in toluene/THF (3:1)) was added to this suspension slowly at -78°C with a steel cannula. The mixture was slowly brought to room temperature under stirring, and an almost black solution was

obtained. This was warmed to 55°C for 20 h. After the mixture had been cooled to room temperature, black rhombic crystals of **1** (220 mg, 0.02 mmol, 38 %) were obtained on the glass wall.

Crystal structure data of **1**: $[Ga_{84}[N(SiMe_3)_2]_{20}][Li(thf)_4]_2[Li_2Br(thf)_6]_2 \cdot 2$ toluene, $M_r = 10892.17$, Crystal dimensions $0.2 \times 0.3 \times 0.4$ mm, triclinic, space group $P\bar{1}$, $a = 24.724(5)$, $b = 25.849(5)$, $c = 39.019(8)$ Å, $\alpha = 88.95(3)^\circ$, $\beta = 71.65(3)^\circ$, $\gamma = 62.30(3)^\circ$, $V = 20712.5(72)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.746$ g cm⁻³, $\mu(\text{MoK}\alpha) = 5.703$ mm⁻¹, $2\theta_{\text{max}} = 47.88^\circ$, 128094 measured reflections, 60258 independent reflections ($R_{\text{int}} = 0.0832$), absorption correction: numerical (min./max. transmission 0.1454/0.4062), $R_1 = 0.0523$, $wR_2 = 0.1451$. Stoe-IPDS diffractometer (MoK α radiation ($\lambda = 0.71073$ Å), 200 K). The structure of **1** was solved by direct methods with SHELXS and SHELXTL (G. M. Sheldrick, Universität Göttingen) and refined against F^2 for all observed reflections. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-134328. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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$[\{\text{Rh}(\eta^5\text{-Ph}_2\text{C}_2\text{B}_9\text{H}_9)(\mu_3\text{-OH})\}_4]$: A Tetrameric Icosahedral Metallocarborane Containing an $\{\text{Rh}(\text{OH})\}_4$ Cubane Cluster**

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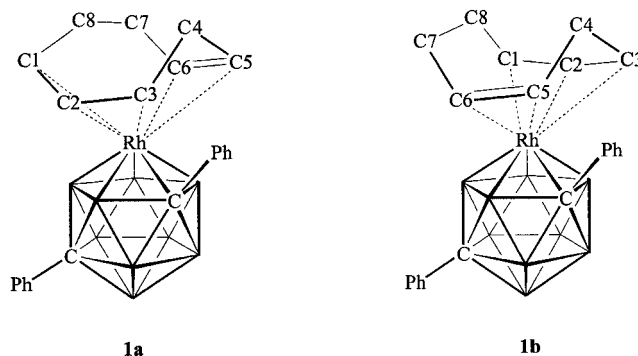
We are currently investigating the mechanism of isomerization of metallocarboranes by inducing low-temperature isomerizations through steric crowding.^[1] Our strat-

egy uses vertex-substitution to follow the movement of specific cluster vertices through the isomerization process since the integrity of the vertex-substituent bond is reasonably assured at low temperatures and thus eventually should provide a complete experimental mapping of the process. Although our initial studies have involved platina-,^[2] molybda-,^[3] and nickeladiphenylcarboranes^[4] we have begun to investigate rhodium species. This has led, fortuitously, to the isolation and characterization of the novel rhodacarborane tetramer described herein.

When $\text{Na}_2[7,8\text{-Ph}_2\text{-}7,8\text{-nido-C}_2\text{B}_9\text{H}_9]$ (prepared in situ from $[\text{HNet}_3][7,8\text{-Ph}_2\text{-}7,8\text{-nido-C}_2\text{B}_9\text{H}_{10}]$ and excess NaH in THF under reflux) is allowed to react with $[\{\text{Rh}(\text{C}_8\text{H}_{12})\text{Cl}\}_2]$ in THF, two new compounds are formed which may be separated by chromatography. The major species **1**, is

$[1,8\text{-Ph}_2\text{-}2\text{-(}1\text{-}3\text{-}\eta^3\text{-}5,6\text{-}\eta^2\text{-C}_8\text{H}_{11}\text{)-}closo\text{-}2,1,8\text{-RhC}_2\text{B}_9\text{H}_9]$ **1**

characterized by ^1H and ^{11}B NMR spectroscopy and by a crystallographic study. The $^{11}\text{B}\{^1\text{H}\}$ NMR spectrum of **1** contains eleven peaks instead of the expected nine between $\delta = +10$ and -15 , the range usually associated with resonance signals from *closo* metallocarboranes. This apparent anomaly was resolved by analysis of ^1H , $^1\text{H}\text{-}^1\text{H}$ correlated (COSY), and $^1\text{H}\text{-}^1\text{H}$ nuclear Overhauser effect (nOe) NMR spectra, which show clear evidence for two conformers (**1a** and **1b**, Scheme 1) which differ in the disposition of the $\eta^3\text{:}\eta^2\text{-C}_8\text{H}_{11}$ ring relative to the carborane cage. Unfortunately it is not possible to establish which conformer is the major component in solution. Subsequent exhaustive thin layer chromatography (tlc) with a variety of eluents could not separate **1a** and **1b**.



Scheme 1. The two conformers of compound **1**. The relative amounts of **1a**:**1b** are approximately 3:1 in the solid state (by X-ray diffraction). In solution (by NMR) there are also two conformers in a 3:1 ratio, but it is not possible to establish which is the major form.

A structural study of **1**^[5] (Figure 1) establishes that low-temperature isomerization has occurred, separating the cage carbon atoms in a $1,2 \rightarrow 1,7$ manner^[1] as in *closo*- $\text{C}_2\text{B}_{10}\text{H}_{12}$. In the crystal the $\eta^3\text{:}\eta^2\text{-C}_8\text{H}_{12}$ ligand is partially disordered (atoms C23 and C25) corresponding to an effective superimposition of conformers **1a** and **1b** in the approximate ratio 3:1.

The direct synthesis of compound **1** is unexpected. Jeffery et al.^[6] have previously obtained the related (but nonisomerized) species $[1,2\text{-Me}_2\text{-}3\text{-(}1\text{-}3\text{-}\eta^3\text{-}5,6\text{-}\eta^2\text{-C}_8\text{H}_{11}\text{)-}closo\text{-}3,1,2\text{-}$

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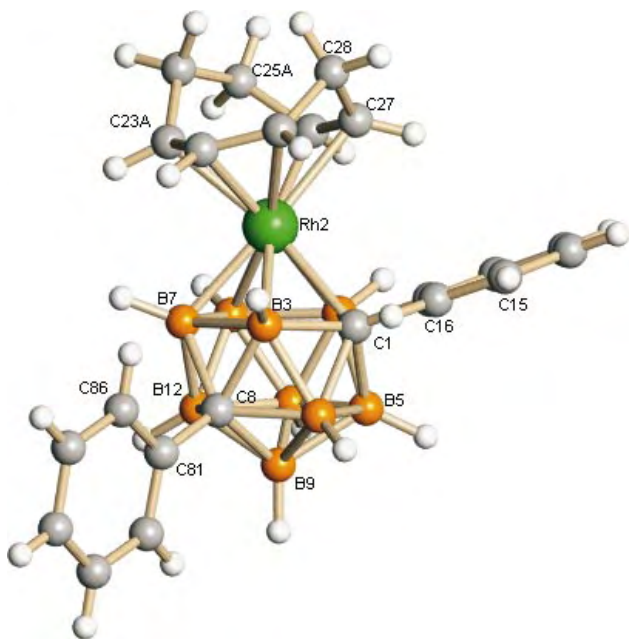


Figure 1. Perspective view of the structure of the major isomer **1a** as determined crystallographically. Selected bond distances [Å] and angles [°]: Rh2-C1 2.268(4), Rh2-B3 2.137(4), Rh2-B7 2.176(4), Rh2-B6 2.189(5), Rh2-B11 2.224(5), Rh2-C21 2.310(4), Rh2-C22 2.196(4), Rh2-C23A 2.217(7), Rh2-C26 2.296(4), Rh2-C27 2.302(4); C21-C22-C23A 123.0(4). C23A and C25A have 76% occupancy. In the minor isomer (**1b**) C23B and C25B (24% occupancy) are nonbonding and bonding to Rh2, respectively; Rh2-C25B 2.215(18), C25B-C26-C27 123.2(8).

RhC₂B₉H₉] by deliberate H[−] abstraction from the ion [1,2-Me₂-3-(1,2-η²-5,6-η²-C₈H₁₂)-*closo*-2,1,8-RhC₂B₉H₉][−]. We believe that **1** also forms from a (nonisolable) η²:η²-C₈H₁₂ containing anionic intermediate but by spontaneous loss of an H[−] ion, presumably to the medium.

Compound **2** forms as a minor by-product in the preparation of compound **1**. The ¹B-¹H NMR spectrum of **2** in CDCl₃ at 298 K shows only five broad, overlapping peaks between δ = +15 and −15, but there is some sharpening and resolution of the spectrum (into seven components) at 333 K. The ¹H NMR spectrum shows only resonance signals assignable to Ph rings which indicates the loss of the C₈ ligand.

The structure of compound **2** was revealed by a crystallographic study (Figure 2).^[7] The molecule is the tetramer [(HO)RhPh₂C₂B₉H₉]₄ composed of four 2,1,8-RhC₂B₉ icosahedra bridged by four μ₃-OH units to give a cubanelike {Rh₄(OH)₄} central core. The tetramer has effective S₄ symmetry (of which C₂ is crystallographically imposed) with alternating 2,1,8-RhC₂B₉ cages of opposite chirality. The results of the crystallographic study suffer from partial disorder of the [(HO)RhPh₂C₂B₉H₉]₄ tetramer parallel to the crystallographic *b* axis ("ghosts" with a 4% occupancy factor ca. 1 Å above and below the major component) and from disordered CH₂Cl₂ and C₅H₁₂ solvate molecules. However, because of mass spectrometric evidence^[8] we are confident that **2** is correctly formulated as [(HO)RhPh₂C₂B₉H₉]₄; **2** can be prepared deliberately by stirring compound **1** with NaOH in THF.^[9]

Compound **2** is the first tetrameric icosahedral metal-lacarborane,^[10] extending in logical sequence this family of

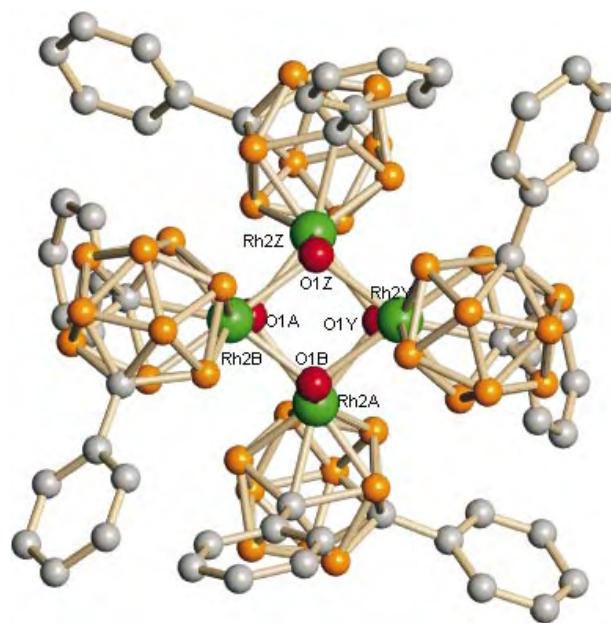


Figure 2. The tetramer **2** viewed down its approximate S₄ axis (crystallographic C₂). For clarity the H atoms are not shown. Selected bond lengths [Å]: Rh2A-O1A 2.249(7), Rh2A-O1B 2.194(9), Rh2A-O1Y 2.142(8), Rh2B-O1A 2.190(8), Rh2B-O1B 2.169(8), Rh2B-O1Z 2.202(9).

compounds from simple monomer (e.g. [CpFeC₂B₉H₁₁]^[11]) through dimer (e.g. [(CO)₂FeC₂B₉H₁₁]₂)^[12] and trimer (e.g. [(Cu(NC₅H₄CO₂Me)₂C₂B₉H₁₀)]₃)^[13]. It is, moreover, the first example of a species with an {M₄(OH)₄} cubanelike core in which M is a Group 9 metal. Structurally and electronically **2** is analogous to the well known species Cp₄Rh₄S₄^[14] (Cp* = C₅Me₅) illustrating further the potential for new chemistry afforded by formal replacement of the five-electron Cp/Cp* ligand with the four-electron carborane ligand.

Experimental Section

[[Rh(C₈H₁₂)Cl]₂] (0.54 mmol) in THF (30 mL) was added to a frozen solution of Na₂[7,8-Ph₂-7,8-*nido*-C₂B₉H₉] (1.08 mmol) in THF (40 mL). After 24 h stirring under N₂ at room temperature solvent was removed in vacuo and the resultant brown powder was dissolved in dichloromethane (5 mL). Initial column chromatography (silica) with dichloromethane: 60/80 petroleum ether (1:1) as the eluent afforded a crude mixture of compounds **1** and **2** as an orange solid (28% yield). Subsequent preparative tlc (silica) of this crude product with 60/80 petroleum ether: dichloromethane (3:2) afforded **1** as yellow (R_f = 0.55) and **2** as orange (R_f = 0.63) products in the approximate ratio 5:1. For **1**: IR (CH₂Cl₂) ν_{max} = 2574 cm^{−1} (s, br; B-H); ¹H NMR (400.1 MHz, CDCl₃, 298 K): δ = 7.7–7.0 (m, Ph), major conformer: 5.86 (ddd, C6-H), 5.28 (ddd, C1-H), 5.00 (dd, C2-H), 3.83 (ddd, C3-H), 3.17 (ddd, C4-H), 2.87 (ddd, C5-H), 2.64 (dddd, C7-H), 2.59 (ddd, C4-H), 2.37 (dddd, C7-H); minor conformer: 5.82 (ddd, C6-H), 5.48 (ddd, C1-H), 4.77 (dd, C2-H), 3.79 (ddd, C3-H), 3.12 (ddd, C5-H), 2.67 (ddd, C4-H), below δ = 2.5 impossible to assign; ¹B-¹H NMR (128.4 MHz, CDCl₃, 298 K): δ = 5.10, 3.61, 2.50, 0.48, −2.22 −3.26, −4.65, −11.01, −11.70, −12.87, −14.20.

2: IR (CH₂Cl₂) ν_{max} = 2586 cm^{−1} (s, br) (B-H); ¹H NMR (400.1 MHz, CDCl₃, 298 K): δ = 7.5–6.9 (m, Ph); ¹B-¹H NMR (128.4 MHz, CDCl₃, 333 K): δ = 12.15, 8.74, 5.13, 4.20, −0.68, −3.83, −10.81.

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Structure and Dynamics of the Host–Guest Complex of a Molecular Tweezer: Coupling Synthesis, Solid-State NMR, and Quantum-Chemical Calculations**

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Supramolecular chemistry and noncovalent interactions are of major importance in many biological systems, for example in enzyme–substrate binding or antigen–antibody recognition, as well as in the design of new materials by molecular self-assembly.^[1] An example is receptor **1**, which belongs to a family of molecules termed “molecular tweezers”, due to their concave–convex topology and their propensity to selectively form complexes with electron-deficient aromatic and aliphatic compounds as well as with organic cations.^[2] This high selectivity has been correlated with a markedly negative electrostatic potential, by using semiempirical and quantum-chemical calculations, for the concave side of the molecular tweezer.^[3]

Hunter and Packer described a supramolecular structure determination, based on the empirical calculation of complexation-induced ¹H NMR shifts in solution^[4] employing the empirical methods^[5] developed for the prediction of ¹H NMR shifts of proteins. As further illustrated by, for example, the study of the dimerization of formic acid in a matrix at 7 to 40 K using IR spectroscopy,^[6] a quantitative elucidation of the structure, dynamics, and electronic properties of such complex systems requires the coupling of advanced techniques of physical characterization and theoretical chemistry. The results of such an endeavour, which we describe here, can then provide guidelines for generating new structures.

Central to our approach are advances in high-resolution ¹H solid-state NMR based on fast magic-angle spinning (MAS).^[7] At rotation frequencies above 30 kHz, sufficient line narrowing is achieved such that ¹H resonances due to chemically distinct protons can be distinguished.^[8] Moreover, fast MAS can be combined with double-quantum (DQ) spectroscopy^[9]

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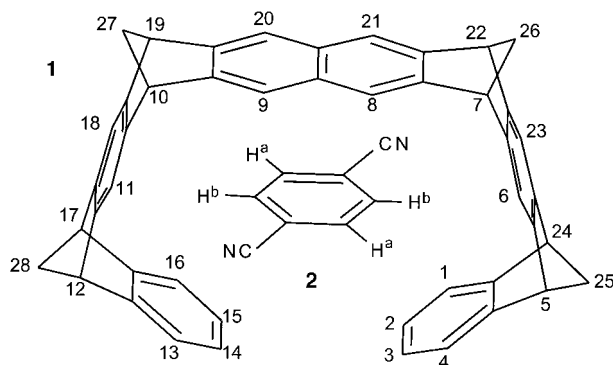
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

to provide access to structural and dynamic information exploiting site-resolved dipolar couplings. This yields specific proton–proton proximity information and allows complex dynamic processes to be quantified. In particular, key elements of supramolecular organization, namely hydrogen bonds and π – π interactions can be clearly unravelled.^[8] Furthermore, the ^1H chemical shifts resulting from supramolecular organization can be assigned quantitatively to specific molecular packing arrangements by means of quantum-chemical calculations.^[10]

To date, molecular tweezer host–guest complexes have been investigated by ^1H solution-state NMR exploiting the large upfield shifts of the substrate resonances, caused by the ring currents due to the aromatic host, upon complexation. For the specific complex studied here, complex formation and dissociation in CDCl_3 at room temperature between the naphthalene-spaced tweezer **1** and 1,4-dicyanobenzene **2** is fast with respect to the NMR timescale, as evidenced



by a single-guest ^1H resonance shifted by 4.35 ppm relative to that observed for **2** alone. A solid-state investigation has the advantage that the guest remains complexed on the timescale of the NMR experiment and, thus, the structure and dynamics of the host–guest complex can be probed directly. An X-ray single-crystal structure is available for **1@2**;^[2b] therefore, this study offers the opportunity to check the reliability of our approach and to demonstrate that additional complementary insight can be provided.

Figure 1a presents a rotor-synchronized ^1H (700 MHz) DQ MAS NMR spectrum of **1@2**. In a ^1H DQ MAS experiment, the evolution of a DQ coherence due to a pair of dipolar-coupled protons is correlated with that of the single-quantum (SQ) coherences of the two individual protons, to allow an unambiguous assignment of pairs of like and unlike protons.^[8] The ^1H solid-state NMR peak assignment (Table 1) follows from a ^1H – ^{13}C heteronuclear correlation^[11] spectrum of **1@2** (Figure 1b), recorded using a recently developed recoupled polarization-transfer (REPT) experiment,^[12] which employs rotational-echo double-resonance (REDOR) recoupling.^[13] Significant differences between the solid- and solution-state ^1H chemical shifts are observed: In particular, the guest protons, which are equivalent in solution, differ in the solid state ($\Delta\delta = 3.6$). This splitting is a strong indication of ring-current effects,^[8b, 14] as discussed below.

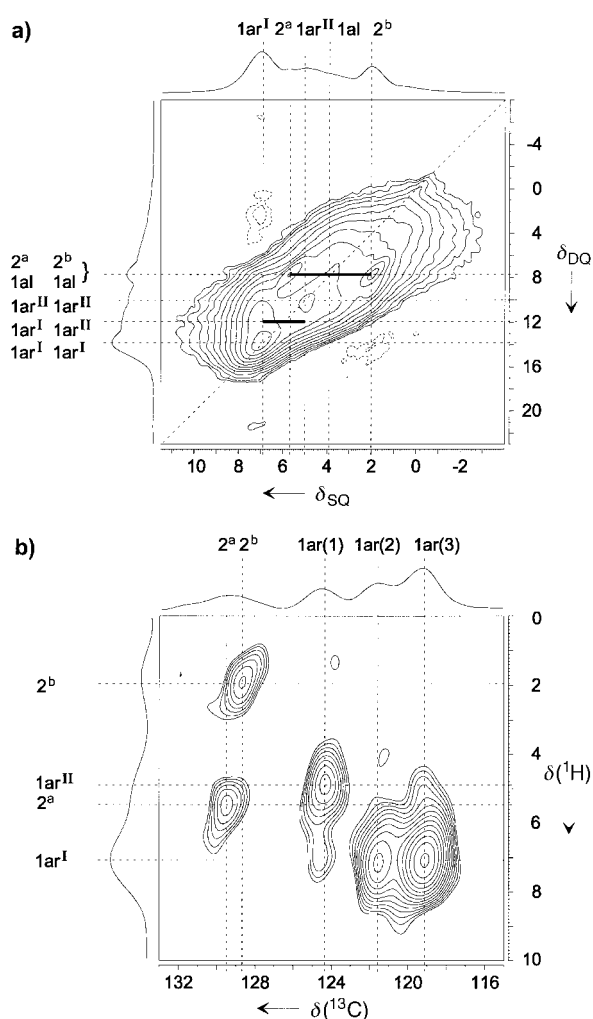


Figure 1. a) Rotor-synchronized ^1H (700.1 MHz) DQ MAS NMR spectrum, together with skyline projections, of **1@2**, recorded under MAS at 30 kHz using one cycle of the BABA recoupling sequence for the excitation and reconversion of DQCs. b) The aromatic region of a ^1H (700.1 MHz)– ^{13}C REPT-HSQC NMR correlation spectrum, together with sum projections, of **1@2**, recorded under MAS at 30 kHz. The recoupling time equaled one rotor period, such that predominantly only one-bond correlations are selected. The sample temperature equalled 321 K in both cases. The notation 1ar and 1al refers to host aromatic and alkyl protons, respectively, while 2^a and 2^b refer to the two distinct guest aromatic protons.

Table 1. Experimental and ab initio ^1H chemical shifts for **1@2**.

	Solution-state NMR	Solid-state NMR	Ab initio (monomer)	Ab initio (dimer)
H^a (guest)	3.5	5.6	5.5	5.2
H^b (guest)	3.5	2.0	2.5	2.1
$\text{H}_{2,3,14,15}$	6.4	4.9	6.6	5.5–5.6
H_{arom} (host)	7.0–7.2	7.1–7.2	7.2–8.0	6.9–7.7
$\text{H}_{\text{bridgehead}}$	4.1	3.8 ^[a]	3.9–4.2	3.3–4.0
$\text{H}_{25,28}$ ^[b]	2.4	2.0–3.8 ^[a]	2.2	2.1
$\text{H}_{26,27}$ ^[b]	2.5	0.6–2.3 ^[a]	2.0–2.1	0.4–1.0

[a] These ^1H chemical shifts were determined from the alkyl region of the ^1H – ^{13}C correlation spectrum (not shown). [b] Note that the two protons in each CH_2 group are inequivalent.

We further performed quantum-chemical calculations to determine the structure and NMR chemical shifts of **1@2**. For the structure determination, we employed newly developed

linear-scaling methods,^[15] at the Hartree–Fock (HF) level. NMR chemical shifts were calculated using the GIAO method (gauge including atomic orbitals)^[16] at the HF level. In this way, we calculate the electronic structure and chemical shifts explicitly, which differs from the (empirical) approach of calculating ring currents.^[17] Table 1 also presents ^1H chemical shifts obtained by the quantum-chemical calculations for a single **1@2** complex and a pair of **1@2** complexes in the arrangement shown in Figure 2a (denoted as monomer and dimer, respectively). The good agreement between the

elsewhere but we note the main conclusions here. Firstly, the guest ^1H chemical shifts, derived by summing the changes due to the separate aromatic moieties, are in good agreement with the values calculated for the whole system. It can thus be concluded that the only influence of the linking norbornadiene units is to determine the positioning of the host aromatic moieties. Secondly, the difference between the guest ^1H chemical shifts is mainly due to the arrangement of the guest with respect to the inner benzene ring (Figure 2c). Thus, our combined experimental and theoretical approach is able

to identify specific intermolecular interactions, which will be particularly useful for the structural elucidation of systems, for which X-ray single crystal structures are not available.

A unique strength of solid-state NMR is its ability to probe molecular dynamics with site selectivity.^[18] Figure 3 presents slices taken from ^1H DQ MAS spectra (each slice at $\delta_{\text{DQ}} = 7.6$) recorded at different temperatures. The peaks due to the guest protons H^a ($\delta = 5.6$) and H^b ($\delta = 2.0$) disappear upon heating, to indicate dynamic processes (see Figure 3), in which the two types of guest protons are exchanged by either a) a 180° flip about the long axis of the guest or b) a 60° rotation between two equivalent sites in the complex. A quantitative analysis is hampered by the peak at $\delta = 3.9$ due to host alkyl protons—the fast exchange peak would be expected to appear at exactly this position. We note, though, that no peak was observed in a slice corresponding to the guest ^{13}C CH resonance in a ^1H – ^{13}C correlation spectrum recorded at 410 K (spectrum not shown). Thus, we conclude that, at this temperature, the exchange process is in the

intermediate regime, namely coalescence. From the difference in the chemical shifts of the guest protons H^a and H^b ($\Delta\delta = 3.6$), the rate constant for the exchange process at 410 K can be estimated to be 5600 s^{-1} corresponding to a Gibbs free enthalpy of activation $\Delta G^\ddagger$ of 72 kJ mol^{-1} .^[19]

To conclude, for the host–guest complex **1@2**, a combined experimental and theoretical approach provides structural information, namely the importance of both intra- and intercomplex interactions as well as the role of the separate aromatic moieties, whereas temperature-dependent solid-state NMR spectra probe the guest dynamics. All experiments were performed on only 10 mg of a powdered sample, without isotopic labeling. Therefore, it is envisaged that solid-state NMR combined with quantum chemistry can become as valuable to the chemist as solution-state NMR is today. The approach described here exploits the sensitivity of ^1H chemical shifts to aromatic ring currents and can be applied to both crystalline and amorphous systems alike. As these effects occur over quite a long range (more than 700 pm),^[10b] we expect such effects to be of general importance in all aromatic systems. It is only now, however,

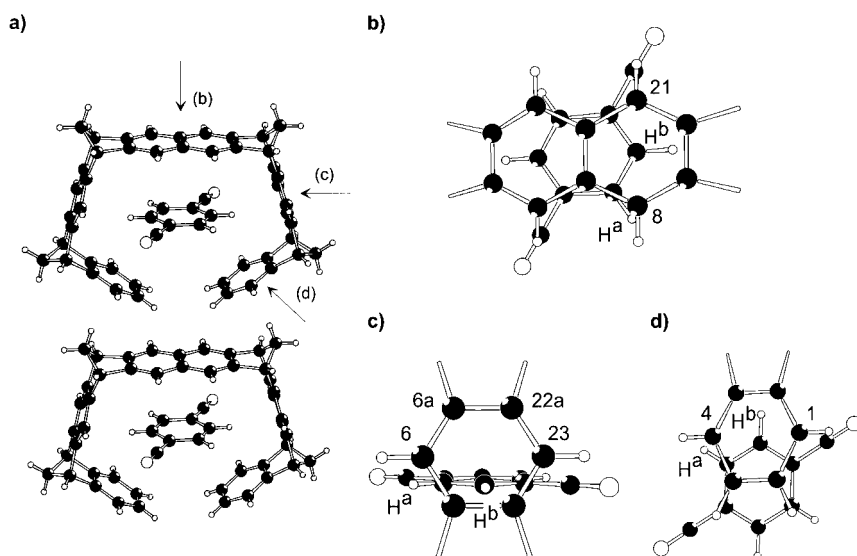


Figure 2. The solid-state packing arrangement of **1@2**, as determined by an X-ray single-crystal investigation.^[2b] Large white, large black, and small white circles represent nitrogen, carbon, and hydrogen atoms, respectively. In b)–d), views through the naphthalene unit (b), and inner (c) and outer (d) benzene rings, respectively, are shown. The distance from H^b to the center of the inner benzene ring is 260 pm, as opposed to 404 pm to the middle of the naphthalene unit and 314 pm to the center of the outer benzene ring (distances are given for the ab initio structure). Specific carbon and hydrogen atoms are labeled according to the above chemical structure; the notation xa refers to the quaternary carbon between carbons x and x + 1.

monomer calculation and the experimental solid-state guest ^1H chemical shifts reveals that these values are largely determined by *intracomplex* effects. We also note that the average deviation in guest-to-host aromatic carbon–carbon distances is less than 5% when comparing the ab initio monomer and X-ray structures. In contrast, the marked difference between the solid- and solution-state ^1H chemical shifts of host aromatic protons (H2,3,14,15) on the “tweezer tip” can only be explained by considering a dimer. *Intercomplex* effects are apparent from Figure 2a, which shows that these pairs of aromatic protons are directed towards the naphthalene unit of the next host. Additional effects of neighbouring monomer units are expected to only be important for the most exposed protons of the tweezer, namely, the CH_2 groups.

Quantum-chemical calculations are able to elucidate the role of different chemical units within a molecule. Therefore, we also calculated the ^1H chemical shifts of the guest protons due to the three host aromatic moieties, namely the central naphthalene unit, and the inner and outer benzene rings (Figure 2b–d). These results will be discussed in detail

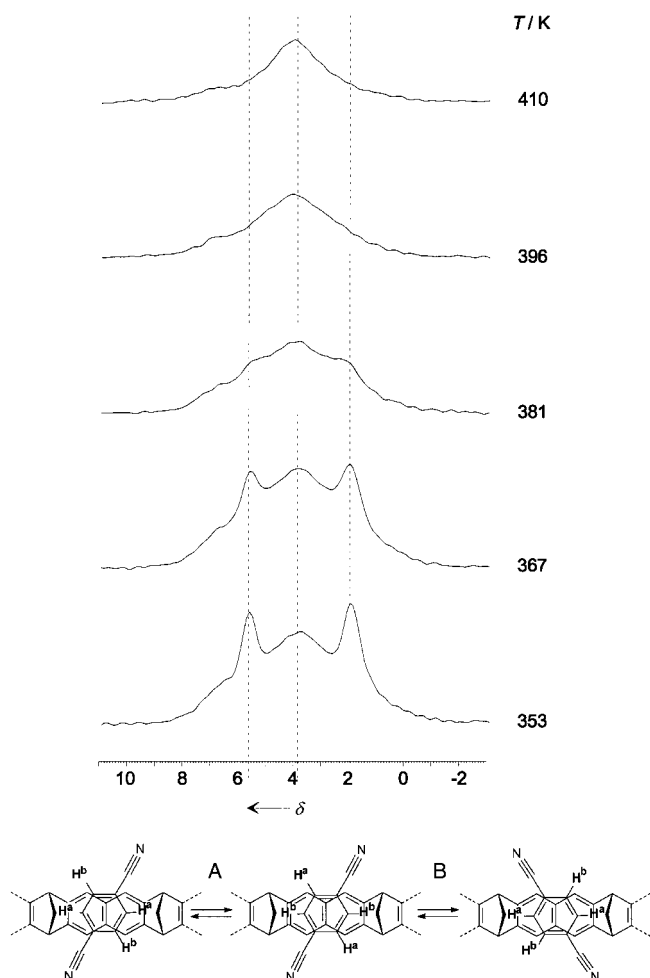


Figure 3. The effect of temperature T on slices ($\delta_{\text{DQ}} = 7.6$) taken from ^1H (700.1 MHz) DQ MAS NMR spectra of **1@2**. At the bottom, the dynamic processes consistent with the observed NMR results are shown. The two processes (A) and (B) cannot be distinguished by current experiments.

that solid-state NMR and quantum chemistry have developed sufficiently to allow the routine experimental observation of the ^1H chemical shifts and the quantitative analysis of intermolecular ring-current effects in relatively large systems, respectively.

Experimental Section

The synthesis of **1** is described in ref. [2b]. The complex with **2** is formed by dissolving the host and guest in a 1:1 molar ratio mixture of methanol/dichloromethane (1/1), followed by evaporation of the solvent at room temperature to yield colorless crystals.

Solid-state NMR experiments were performed on a Bruker DRX700 narrow-bore spectrometer operating at ^1H and ^{13}C Larmor frequencies of 700.1 and 176.1 MHz, respectively, with a double-resonance 2.5 mm MAS probe, 90° pulse lengths of 2.0 μs on both channels, and a recycle delay of 1 s. In all spectra, the increment in t_1 was set equal to one rotor period. For the DQ MAS [REPT-HSQC] experiment, for each of the 64 [24] increments, 16 [1024] transients were averaged. In the contour plots (Figure 1a, b), solid and dashed lines represent positive and negative contours, respectively; the bottom contour corresponds to 2.0 and 8.0 % of the maximum intensity (in Figure 2a, b) and subsequent contours corresponding to a multiplicative increment of 1.4 and 1.2.

Quantum-chemical calculations^[10] were performed with the packages Q-Chem and TURBOMOLE.^[20] The structure of **1@2** was optimized at

the Hartree–Fock (HF) level employing a 6-31G* basis.^[21] ^1H chemical shifts were calculated using the GIAO method at the HF level, and are given relative to tetramethylsilane (TMS). For the monomer calculation, a (triple- ζ polarization (TZP) basis was used.^[22] The dimer was constructed by arranging two **1@2** complexes (with the optimized quantum-chemical structure) at a separation given by the single-crystal structure.^[2b] Dimer correction values were obtained as the difference between the dimer and monomer ^1H chemical shifts at the GIAO-HF/SVP^[22] level; these values were added to the monomer values calculated at the GIAO-HF/TZP level. The dimer ^1H chemical shifts are given in Table 1. The ^1H absolute shieldings for TMS (calculated at HF/6-31*) are $\delta = 32.4$ (GIAO-HF/TZP) and 32.3 (GIAO-HF/SVP).

The solution-state NMR assignments, as well as additional details concerning the experimental solid-state NMR and quantum-chemical calculations, are provided as Supporting Information.

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Subtleties with Sulfur: Calixarenes as Uranophiles**

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Evidence that support of donor atoms on a calixarene scaffolding might provide selectivity in the binding of U^{VI} , putatively as UO_2^{2+} ,^[1] has led to interest in establishing the coordination mode of uranium in such species.^[2] Early work^[3, 4] on the synthesis of UO_2^{2+} -specific ligands, so-called "uranophiles",^[5, 6] presumed that ligands providing essentially planar pentagonal or hexagonal donor atom arrays would be most apposite, given that such geometries, common in UO_2^{2+} complexes, are not well known for other metal ions.^[7] This argument was advanced^[1] as a possible explanation of selective binding of UO_2^{2+} by a number of (water-soluble) calix[6]arene derivatives, though the focus was more on the geometry than the dimensions and nature of the donor set. Indeed, the suggestion that six phenoxide donors might be involved seems at variance with the known chemistry of UO_2^{2+} with alkoxide ligands,^[8] where only four such ligands are found in species of near-octahedral symmetry. True U^{VI} alkoxides, $[U(OR)_6]$, are known^[8] but are not stable under the conditions used to form uranyl ion/calixarene complexes by solvent extraction, though there may be exceptional formation of such species by a calix[6]arene ligand. Significantly, however, the recent structural characterization of a pyridine-stabilized U^{VI} derivative of *p*-*t*Bu-calix[6]arene^[9] shows two ligand molecules are required to give octahedral coordination, each of which functions as a tridentate donor in a 1,2,3-*alternate* conformation.

In crystal structures of UO_2^{2+} complexes of calixarenes with only phenoxide donors, a maximum of four equatorial phenoxide groups is found.^[2] Trigonal coordination is seen in the complex of the expanded calixarene, *p*-*t*Bu-hexahomotrioxa-calix[3]arene,^[10] suggesting a different possible approach to the synthesis of uranophiles to that based on attaining unusual, high-coordination geometries, though it is

not known if this complex is more stable than those obtained with *p*-*t*Bu-dihomooxalix[4]arene,^[11] *p*-*t*Bu-calix[6]arene^[12] or *p*-*t*Bu-calix[7]arene,^[13] which display approximately square-planar coordination. (In the complex of *p*-*t*Bu-calix[5]arene,^[14] a phenol OH unit functions as a fifth donor in a strongly distorted pentagonal-planar array.) It may be that the determinant of UO_2^{2+} bonding to calixarenes, regardless of selectivity, is the optimal U–O(phenoxide) separation; data from structures of U^{VI} compounds with unrestricted (unidentate) alkoxide ligands provide an estimate of about 2.2 Å as the "ideal" such distance.^[2] Here, we present structures for the hitherto uncharacterized UO_2^{2+} /calix[4]arene system and the UO_2^{2+} complex of *p*-*t*Bu-tetrathiocalix[4]arene. These illustrate how quite subtle changes in ligand geometry can drastically alter the form of complexes. In the first case, the structure is that of the uranyl ion complex of calix[4]arene itself,^[15a] the smallest methylene-bridged calixarene. In the second case, the structures of two different solvates^[15b,c] of the UO_2^{2+} complex of *p*-*t*Bu-tetrathiocalix[4]arene,^[16] which is apparently generally superior to its CH_2 -bridged analogue as a metal binding agent. Structural evidence shows that, at least in some cases, this should be associated with coordination of the thiaether sulfur atoms.^[17, 18] Paradoxically, the UO_2^{2+} complex structures are the first of a diversity determined by us in which there is no metal–S interaction.

The structure of the stoichiometric unit of the UO_2^{2+} /calix[4]arene complex is shown in Figure 1. Ignoring the

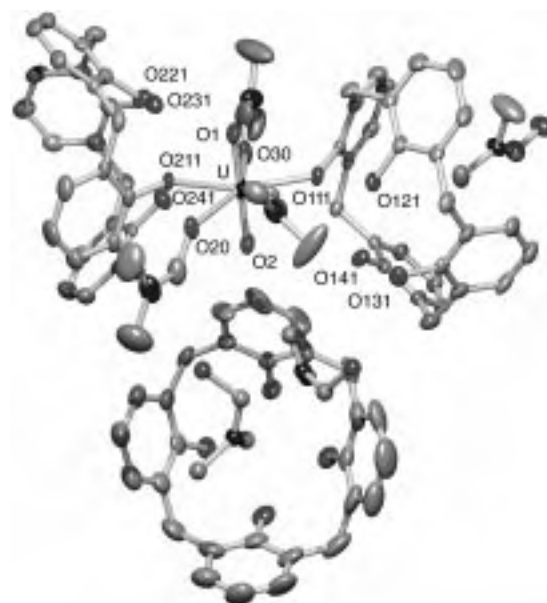


Figure 1. Structure of $[UO_2\{(calix[4]arene-H)(dmf)\}(calix[4]arene-H)(dmf)_2.7(dmso)_{0.3}]\cdot 1/2 DMF$. U–O(1,2; 111,211; 10,20,30) 1.753(3), 1.755(3); 2.358(3), 2.396(3); 2.399(3), 2.400(3), 2.368(3) Å. O...O distances in the calixarene (cyclically from O(m11): 2.747(4), 2.779(4), 2.912(4), 2.691(4), ($m=1$); 2.718(4), 2.740(4), 2.978(4), 2.732(4) ($m=2$); 2.658(5), 2.678(5), 2.626(5), 2.663(5) Å ($m=3$). C_6 dihedral angles between the six-membered rings and the relevant O_4 planes: $m=1$ ($\chi^2=10^4$; deviations from the average plane: $\delta(On1)$ 0.181(4), –0.189(4), 0.208(4), –0.196(4); $\delta(U)$ 2.382(3) Å): 63.1(1), 39.8(1), 72.0(1), 49.4(1)°; $m=2$ ($\chi^2=6\times 10^3$; $\delta(On1)$ 0.129(4), –0.160(4), 0.154(4), –0.157(4); $\delta(U)$ 2.229(3) Å): 64.0(1), 40.0(1), 70.0(1), 55.8(1)°; $m=3$ ($\chi^2=53$; $\delta(On1)$ 0.014(4), –0.017(5), 0.018(5), –0.015(4) Å): 54.8(2), 60.0(2), 52.6(2), 55.0(2)°.

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disorder associated with the mixture of neutral, unidentate (solvent) ligands present, the cause of earlier failures to isolate complexes, principally of *p*-*t*Bu-calix[4]arene but also of calix[4]arene, may lie in the limited interaction with the calixarene suggested by its mere unidentate coordination. Although influenced by hydrogen bonding involving residual phenolic protons, the 1,3-oxygen atom separation is less than twice the “ideal” U–O(phenoxide) distance (4.4 Å). Thus, if the observed conformation is an indicator of that adopted by the fully deprotonated ligand, envelopment of UO_2^{2+} by provision of four “equatorial” phenoxide donors may not be possible. For a simple calixarene^[19] with pendent donors (cf. some biological systems^[20]) variable donor atom separation can result from tilting of the units to which they are attached.^[21] Here, however, it seems a sufficient tilt to span UO_2^{2+} is energetically too demanding. The relatively long U–O(phenoxide) bonds indicate that when full deprotonation of a calixarene is not achieved, hydrogen bonding with residual phenolic units may reduce the donor strength of formal phenoxide donors.

In contrast, in the analogue of *p*-*t*Bu-calix[4]arene in which the CH_2 bridge is replaced by S, the macrocycle expansion of about 0.5 Å per “edge”, which is defined by the distance between two adjacent bridging atoms, is apparently sufficient to allow accommodation of the needs of UO_2^{2+} . A 1:1 complex is readily obtained, the synthesis being insensitive to the presence of water, whereas with *p*-*t*Bu-calix[4]arene—and to a certain extent with calix[4]arene—the basic conditions employed lead to the ready precipitation of $\text{UO}_2(\text{OH})_2$ through traces of water present in “dry” solvents.^[2] The structure of the thiacalixarene complex is shown in Figure 2.

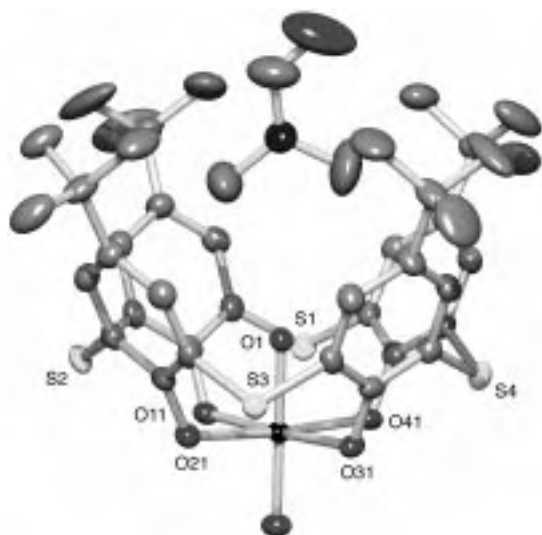


Figure 2. Structure of $[\text{UO}_2\{(p\text{-}t\text{Bu-tetrathiacalix[4]arene} - 4\text{H})(\text{dmf})\}] \cdot 2\text{DMF}$ array, projected quasi-normal to the cone axis, and showing the included DMF molecule. U–O(1,2; 11–41) 1.788(2), 1.804(2); 2.300(2), 2.230(2), 2.293(2), 2.241(2) Å. Dihedral angle between the six-membered rings and the O_4 plane ($\chi^2 = 5 \times 10^2$; $\delta(\text{O}11)$ (alternately) $\pm 0.024(2)$; $\delta(\text{U})$ 0.077(1) Å): 64.29(7), 59.98(7), 63.89(7), 62.05(7)°. While the U–O distance for the MeCN/DMSO solvate lie within 3σ (σ = standard deviation) of the value of the DMF solvent (exception: U–O(21) 2.260(4) Å), the $\text{C}_6\text{--O}_4$ dihedral angles are appreciably larger (67.2(2), 64.4(2), 67.8(2), 64.6(2)°), suggesting that inclusion of the “larger” DMF ligand is accommodated by “flattening” of the cone.

The coordination geometry of uranium is similar to that in each uranium center of the dinuclear UO_2^{2+} complex with *p*-*t*Bu-calix[6]arene and is close to a regular octahedral form, as in $\text{UO}_2(\text{OR})_4$ complexes. Interestingly, the insertion of one UO_2^{2+} oxygen atom into the calixarene cavity does not prevent the inclusion of solvent molecules. The UO_2^{2+} –oxygen bond lengths are significantly shorter than in the corresponding calix[4]arene species, which perhaps reflects more effective charge donation in the equatorial plane by the four phenoxide donors.

Experimental Section

$[\text{HNEt}_3]_2[\text{UO}_2\{(p\text{-}t\text{Bu-tetrathiacalix[4]arene} - 4\text{H})(\text{MeCN})\}] \cdot \text{ca. } 1.7\text{DMSO}$: *p*-*t*Bu-Tetrathiacalix[4]arene $\cdot \text{CHCl}_3$ (0.11 g, 0.13 mmol) was dissolved in DMSO (1.5 mL) containing NEt_3 (0.1 mL) and mixed with a solution of $[\text{UO}_2(\text{dmsO})_5](\text{ClO}_4)_2$ (0.10 g, 0.13 mmol) in DMSO (1.5 mL). Vapor diffusion of MeCN into this deep red solution in a closed vessel over three days provided large, red plates. A single crystal was selected for structure determination, and the residual solid was collected by filtration, washed with MeCN, and air-dried (100 mg, 56%). Elemental analysis indicated some loss of DMSO from the bulk relative to the single crystal: calcd (%) for $[(\text{CH}_3\text{CH}_2)_3\text{NH}]_2[\text{UO}_2\{(\text{C}_{40}\text{H}_{44}\text{O}_4\text{S}_4)(\text{MeCN})\}] \cdot \text{C}_2\text{H}_6\text{SO}$: C 51.32, H 6.54, N 3.21, S 12.23; found: C 51.4, H 6.0, N 3.2, S 11.2; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ = 1.10 (s, *t*Bu), 1.49 (t, Me, NEt_3), 1.55 (s, MeCN), 2.57 (s, DMSO), 3.26 (q, CH_2 , NEt_3), 7.62 (s, aryl-H); IR (KBr): $\tilde{\nu}$ = 3429 (NH), 2693 (CH), 826, 797 cm^{-1} (U=O).

$[\text{HNEt}_3]_2[\text{UO}_2\{(p\text{-}t\text{Bu-tetrathiacalix[4]arene} - 4\text{H})(\text{dmf})\}] \cdot 2\text{DMF}$: *p*-*t*Bu-Tetrathiacalix[4]arene $\cdot \text{CHCl}_3$ (0.10 g, 0.19 mmol) was dissolved in DMF (3 mL) containing NEt_3 (0.1 mL) and mixed with a solution of $[\text{UO}_2(\text{NO}_3)_2(\text{OH})_2] \cdot 5\text{H}_2\text{O}$ (0.17 g, 0.20 mmol) in DMF (3 mL). The deep orange-red solution formed was placed in a closed vessel for three days, which led to deposition of large red plates. A specimen was removed for the X-ray work and the bulk was isolated as above (100 mg, 73%). Elemental analysis indicated partial desolvation: calcd (%) for $[(\text{CH}_3\text{CH}_2)_3\text{NH}]_2[\text{UO}_2\{(\text{C}_{40}\text{H}_{44}\text{O}_4\text{S}_4)(\text{C}_3\text{H}_7\text{NO})\}] \cdot \text{C}_3\text{H}_7\text{NO}$: C 52.08, H 6.78, N 4.19, S 9.59; found C 51.6, H 6.6, N 3.7, S 9.7; IR (KBr): $\tilde{\nu}$ = 3430 (N–H), 2957, 2651, 2489 (C–H), 833, 796 cm^{-1} (U–O).

$[\text{UO}_2\{(\text{calix[4]arene} - \text{H})(\text{dmf})\}(\text{calix[4]arene} - \text{H})(\text{dmf})_{2.7}(\text{dmsO})_{0.3}] \cdot [\text{calix[4]arene}(\text{dmf})] \cdot 1/2\text{DMF}$: Calix[4]arene (106 mg) was dissolved in DMF (2 mL) containing $\sim 1\text{M}$ methanolic NMe_4OH solution (0.5 mL) and mixed with a solution of $[\text{UO}_2(\text{dmsO})_5](\text{ClO}_4)_2$ (220 mg) in DMF (1 mL). The deep red-orange solution formed was placed in a vapor diffusion cell along with 2-propanol. A heterogeneous deposit of colorless and orange material was obtained. On extended standing (1 year) of this mixture, an orange crystal appropriate for an X-ray study was removed, whose structure modeled the composition given above.

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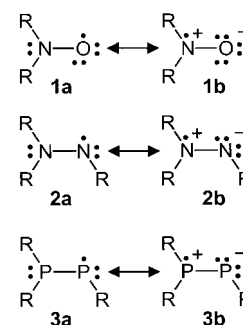
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Isolation of a Highly Persistent Diphosphanyl Radical: The Phosphorus Analogue of a Hydrazyl**

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Despite the enormous importance of radicals in both chemical reactions and biological processes, very few organic free radicals have been isolated.^[1, 2] Notable exceptions are nitroxides **1** and hydrazyls **2**, in which the unpaired electron is localized on a nitrogen center.^[3] These stable radicals, which are described by the resonance structures **a** and **b** (Scheme 1), are applied as contrast agents, molecular markers, and reporters for molecular movements (spin labels).^[4] Considerable effort has been invested in the synthesis of stable free radicals localized on phosphorus, the closest homologue to nitrogen.^[5–9] Indeed, this element consists of only one isotope, ³¹P, with a nuclear spin of 1/2 giving rise to a hyperfine coupling which is much larger than with the nitrogen isotope ¹⁴N. This property is particularly interesting for spin-labeling experiments, since the anisotropy (orientation dependence) of the hyperfine coupling with ³¹P would provide detail concerned



Scheme 1. Resonance structures **a** and **b** of nitroxide **1**, hydrazyl **2**, and diphosphanyl **3**.

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with much faster molecular movements than that available from nitroxides **1**. We report here a synthesis of a phosphorus analogue (**3**) of hydrazyls **2** and show that the anisotropy of the hyperfine coupling is very large, indeed.

Our synthetic route begins with the phosphonium salt $[\text{Mes}^*\text{MeP}=\text{PMes}^*]^+(\text{O}_3\text{SCF}_3)^-$ (**4**; $\text{Mes}^* = 2,4,6\text{-}t\text{Bu}_3\text{C}_6\text{H}_2$), which contains a strong P–P double bond.^[10] Its cyclic voltammogram (Figure 1) shows that **4** undergoes two suc-

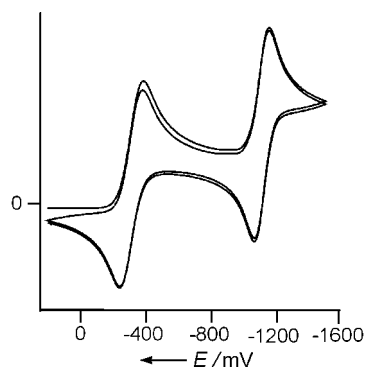
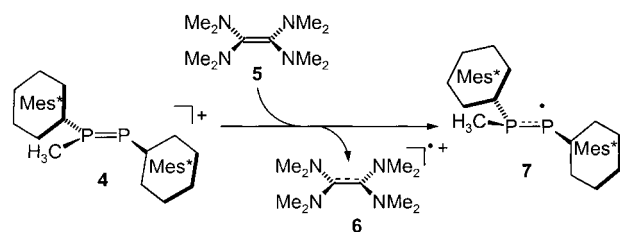


Figure 1. Cyclic voltammogram of a ca. 10^{-4} M solution of **4** in acetonitrile containing 0.1 mol L^{-1} $n\text{Bu}_4\text{NPF}_6$ as electrolyte. Potentials versus Ag/AgCl, scan rate 100 mV s^{-1} .

cessive chemically reversible single-electron reductions at potentials ($E_{1/2}^1 = -0.37 \text{ V}$, $E_{1/2}^2 = -1.23 \text{ V}$ vs. Ag/AgCl) that are about 1 V lower than the ones of usual phosphonium salts.^[11] The first step corresponds to the formation of the diphosphenyl radical $[\text{Mes}^*\text{MeP}=\text{PMes}^*]^\bullet$ (**7**) and the second to the formation of the phosphanyl phosphide anion $[\text{Mes}^*\text{MeP}=\text{PMes}^*]^-$ (**8**).

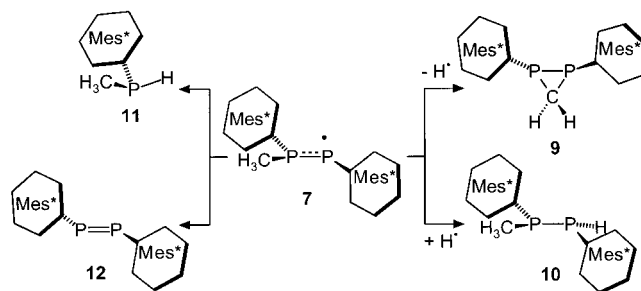
The ease with which **4** can be reduced prompted the chemical synthesis of radical **7** by a simple electron transfer reaction using tetrakis(dimethylamino)ethylene (TDE) (**5**) as electron donor ($E_{1/2}(\text{TDE}^{2+}/\text{TDE}) \approx -0.55 \text{ V}$ vs. Ag/AgCl; Scheme 2).^[12] At the interface of the yellow acetonitrile



Scheme 2. Synthesis of radical **7**.

solution of **4** layered with a solution of **5**, the color turns immediately green. Simultaneously, the characteristic red color of the stable radical cation TDE^{2+} **6** appears. Furthermore, yellow-orange crystals form on the wall of the reaction flask. Optimization of the reaction conditions yields crystals of **7** by filtration after a reaction time of 3 min. Radical **7** is soluble in *n*-hexane giving rise to an intense green solution (UV/Vis: $\lambda_{\text{max}} = 668 \text{ nm}$). The EPR spectrum of this solution shows a simple four-line pattern due to coupling of the unpaired electron with two inequivalent ^{31}P nuclei proving the

identity of **7** as a diphosphenyl radical.^[6, 7] Magnetic measurements of crystals of **7** indicated that the radical exists up to about 90% as monomer and that the crystals are contaminated by solvent (MeCN). In the solid state, radical **7** is stable at temperatures below -30°C for several days, but decomposes at room temperature slowly both in the solid state and in *n*-hexane solution ($t_{1/2} \approx 90 \text{ min}$ at $3 \times 10^{-2} \text{ mol L}^{-1}$) as can be monitored by the fading of the green color. The decomposition products are shown in Scheme 3. The diphosphirane **9**^[10] (ca. 30%) and diphosphane **10**^[13] (ca. 43%) are formally the products of a disproportionation reaction, while phosphane **11**^[14] (ca. 17%) and diphosphene **12**^[15] (ca. 10%) most likely stem from cleavage of the P–P bond and cleavage of the P–P bond followed by dimerization.



Scheme 3. Decomposition of radical **7**.

So far, we have not been able to obtain crystals of **7** suitable for an X-ray analysis. However, a combination of solid-state EPR experiments and theoretical methods unambiguously determined the structure of **7**. Diphosphenyl **7** can be incorporated into the lattice of single crystals of the diphosphane $\text{Mes}^*\text{MeP}=\text{PMes}^*\text{Me}$ (**13**).^[10] Crystals of pure **13** are yellow but become deep green when doped with **7**. Such crystals can be stored at room temperature without notable decomposition of **7** and can even be handled in air. The angular dependence of the EPR signals recorded with such a crystal shows that the paramagnetic species **7** is indeed trapped in the guest lattice ($g_{\text{average}} = 2.008$). Owing to the symmetry of the host lattice, two magnetically inequivalent orientations of **7** are detected, each of which gives rise to a four-line pattern (Figure 2).

The resulting anisotropic ^{31}P coupling constants are listed in Table 1. A comparison with atomic constants^[16] indicates that the unpaired electron is essentially confined to phosphorus p orbitals, with a larger spin density on P1 than on P2. The isotropic couplings ($A_{\text{iso}}(\text{P1}) = 250 \text{ MHz}$, $A_{\text{iso}}(\text{P2}) = 390 \text{ MHz}$) show that the s character of the orbital containing the unpaired electron remains modest: $\rho_s(\text{P1}) = 0.019$, $\rho_s(\text{P2}) = 0.029$. Furthermore, the complete molecule **7** was optimized by using the Amsterdam Density Functional (ADF 2.3) suite of programs^[17, 18] and these results are also given in Table 1. Figure 3 shows the calculated structure overlaid with a graphical representation of the spin density. The agreement between the experimental and calculated anisotropic coupling constants is excellent; in particular, the experimentally

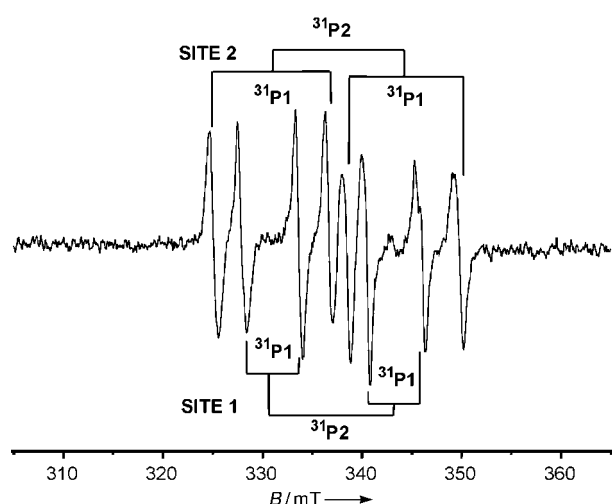


Figure 2. EPR spectrum of a single crystal of Mes*MeP-PMes*Me (**13**) doped with Mes*MeP-PMes* (**7**). Due to the crystal symmetry, the radical is trapped along two magnetically inequivalent orientations (site 1 and site 2).

Table 1. Experimental and calculated anisotropic hyperfine coupling constants τ_1 – τ_3 [MHz], and spin densities ρ_p . The average of the g tensor = 2.008.

Atom	ρ_p [%]	τ_1	τ_2	τ_3
P1 in 7	62 ^[a]	–243	–214	457
P2 in 7	15 ^[a]	–64	–48	113
P1(calcd)	74	–233	–222	456
P2(calcd)	15	–73	–60	133

[a] Determined by comparison with atomic coupling constants.

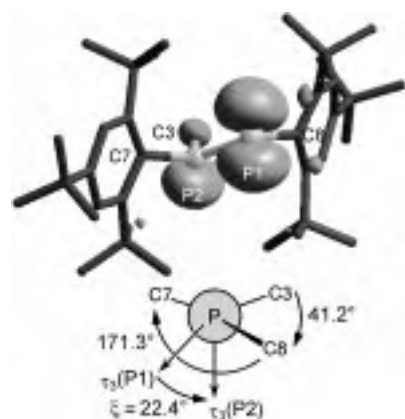


Figure 3. Geometry-optimized structure of **7** and graphical representation of the spin density distribution. Selected bond lengths [Å] and angles [°]: P1–P2 2.18, P1–C8 1.89, P2–C3 1.88, P2–C7 1.89; P2–P1–C8 96.1, C3–P2–P1 115.3, C7–P2–P1 116.3.

determined angle ($\xi = 25^\circ$) between the two “parallel” ^{31}P -eigenvectors is close to the calculated value ($\xi = 22.4^\circ$).

It is interesting to compare the structure of **7** with that of 1,2-diphenylpicrylhydrazyl (DPPH). In this nitrogen radical the ξ angle is 13° , the N–N bond length lies between that of a single and of a double bond (bond order 1.5), and the three-coordinate nitrogen center lies in a planar coordination sphere. This is in contrast with **7** in which the P–P bond length

(2.18 Å) approaches that of a P–P single bond (~ 2.22 Å), and the phosphorus center P2 resides in a pyramidal environment. Interestingly, the degree of pyramidalization in **7** ($\Sigma(\text{P2})$: 337.5°) is almost exactly halfway between the one in **4** (planar, $\Sigma(\text{P2})$: 360°) and the more pronounced one in **13** ($\Sigma(\text{P})$: 315.9°), and agrees well with the one observed in the singlet diradicals (1,3-diphosphacyclobutane-2,4-diyl) [RPCR^1]₂ ($\Sigma(\text{P})$: 337 – 341°) synthesized by Niecke et al.^[19] Like in the latter, some degree of π donation from P2 to the electron-deficient center, here P1, may be assumed. The structural features of **7** are responsible for a large spin localization on P1, whereas in the nitrogen analogue the unpaired electron is almost equally delocalized over the two nitrogen centers. As expected, the anisotropy of the EPR spectrum is considerably more pronounced for the diphosphanyl radical **7** than for the nitrogen-centered hydrazyl species. For **7**, the low-field and high-field transitions are separated by 42 mT when the magnetic field H_0 is oriented along the magnetic $3p_z$ orbital of P1 and by only 13 mT for H_0 perpendicular to this direction. The corresponding anisotropy (820 MHz)—superior to that of DPPH (230 MHz) or nitroxides (150 MHz)—indicates that diphosphanyl radicals are well suited for the study of fast molecular movements.

The work described here demonstrates that diphosphanyl free radicals are much more stable than previously thought and can be isolated. Elucidation of the principal structural and physical properties in connection with the discovery of possible decomposition pathways will help to rationalize possible substitution patterns in [$\text{RR}^1\text{P-PR}^2$]-type radicals to further enhance the stability of diphosphanyls.

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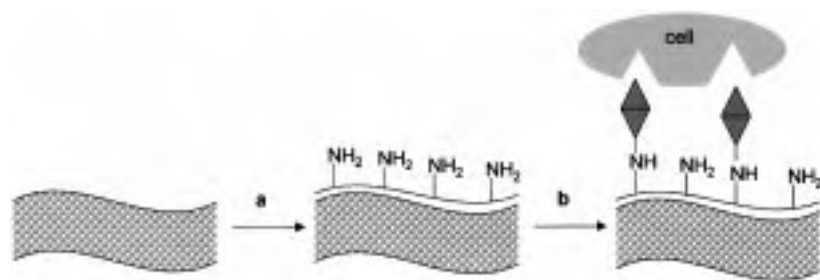
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Synthesis of Amino[2.2]paracyclophanes—Beneficial Monomers for Bioactive Coating of Medical Implant Materials**

Jörg Lahann, Hartwig Höcker, and Robert Langer*

Substituted [2.2]paracyclophanes have received increasing interest over the past few years.^[1] Beside their use as chiral auxiliaries for asymmetric synthesis^[2] and as ligands in metal clusters,^[3] they were reported to be suitable monomers for chemical vapor deposition (CVD) polymerization.^[4] CVD-based polymer coatings were of interest as interfaces for biomedical applications due to their potential for the incorporation of functional groups (Scheme 1). These functional groups can be used to conjugate biomolecules such as proteins, antigens, or cell receptors to implant surfaces.^[5] The resulting biomimetic coatings provide interfaces that may allow control of the interactions between biomaterials and organisms. There is an increasing demand for bioactive



Scheme 1. Concept of bioactive coating for tissue engineering based on CVD polymerization of amino[2.2]paracyclophanes. a) CVD polymerization of amino[2.2]paracyclophane provides a reactive interface. b) Linkage of cytokines to the interface, for example cell receptors, growth factors, antigens, or cell adhesion mediators, controls interactions with cells.

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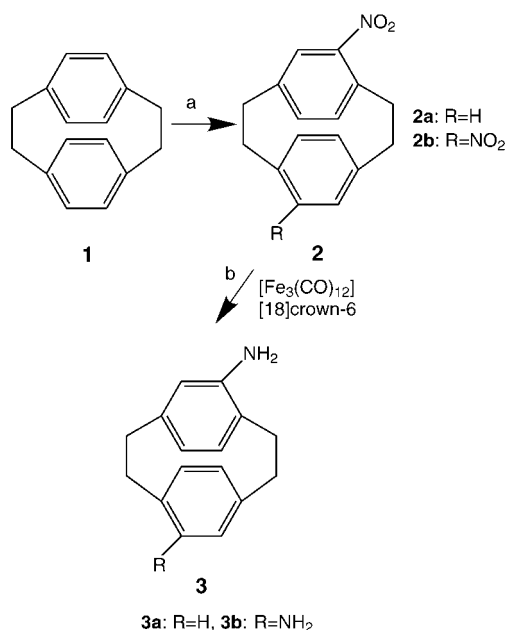
surfaces, particularly in rapidly growing fields such as tissue engineering.^[6]

Several substituted [2.2]paracyclophanes were reported to undergo CVD polymerization.^[7] Although amino-substituted polymers are interesting polymers for biomedical applications, their synthesis by CVD is limited by the lack of facile and effective syntheses of amino-functionalized [2.2]paracyclophanes. 4-Amino[2.2]paracyclophane (**3a**) is commonly synthesized from **1** by a five-step synthesis^[8] via [2.2]paracyclophanecarboxylic acid and Curtius rearrangement. This synthesis provides poor yields of **3a**, and diamino[2.2]paracyclophane (**3b**) has yet to be synthesized following this approach. Alternatively, **3a** was recently prepared from 4-bromo[2.2]paracyclophane by metalation with butyllithium and successive amination in 46 % yield.^[9] The direct synthesis of amino[2.2]paracyclophanes by nitration and subsequent reduction of the nitro[2.2]paracyclophanes suffers from the poor resistance of [2.2]paracyclophanes to oxidation and its tendency to polymerization. In early studies, Cram et al. reported the synthesis of nitro[2.2]paracyclophanes by treatment of [2.2]paracyclophane with mixtures of nitric acid and sulfuric acid that resulted in yields of 26 % for the mononitro compound **2a** and of 8 % for the dinitro product **2b**.^[10] In addition to poor yields, purification of the products from polymeric by-products was difficult, which limited the broad application of this route. Herein we describe a new convenient high-yield synthesis route to **3a** and **3b**.

Treatment of anhydrous nitric acid with trifluoromethanesulfonic acid delivers free nitronium ions^[11] which exhibit high nitration power even at low temperatures (Scheme 2). We found that **1** is completely nitrated at temperatures as low as -78°C . Due to the low temperatures and short reaction times, side reactions like oxidation or polymerization of **1** are not favored and were not observed. As a result, yields of the nitro[2.2]paracyclophane **2b** were increased from 8 % to 93 %.

These nitration conditions could be adjusted to synthesize selectively either **2a** or **2b**. Using the superacidic ion-exchange resin Nafion/nitric acid, **2a** is obtained in 95 % yield. Synthesis of dinitro[2.2]paracyclophane **2b** is best carried out with stirring for 30 min at -78°C and an additional 2 h at -20°C . Only traces of **2a** were found under these conditions. The main product **2b** (93 %) was determined to comprise mainly the pseudo-*para* isomer **2b'** (75 %), with about 25 % of the pseudo-*meta* isomer (**2b''**). Other isomers were less than 2 %, as shown by gas chromatography. This ratio was not affected by the subsequent reduction and is responsible for the fact that **3b** contains 22.7 % pseudo-*meta* diamino[2.2]paracyclophane (**3b''**) (Table 1).

Reduction of the nitro[2.2]paracyclophanes was previously carried out with hydrogen using platinum catalysts.^[12] However, these reaction conditions are unfavorable and yields are low to moderate. Therefore, more efficient routes are necessary if amino-substituted [2.2]paracyclophanes are to be exploited as potential monomers for CVD. Several



Scheme 2. Synthesis of amino- and diamino[2.2]paracyclophanes **3** (for the disubstituted compounds the pseudo-*meta* isomer is shown). a) Trifluoromethanesulfonic acid/nitric acid (1:1, 100%), dichloromethane, low temperature, or nafion/nitric acid (100%), dichloromethane, room temperature; b) phase-transfer catalysis, toluene/aqueous KOH (1N), room temperature.

Table 1. ¹H NMR chemical shifts of aromatic protons in **3a** and **3b**.

	Yield ^[a] [%]	<i>ortho</i>	<i>meta</i>	<i>para</i>	pseudo- <i>ortho</i>	pseudo- <i>meta</i>	pseudo- <i>para</i>	pseudo- <i>geminal</i>
3a	95	5.38	6.18	6.05	6.32	6.32	6.51	7.08
3b'	68.5	5.44	6.17	6.58	6.17	5.44	–	6.58
3b''	22.7	5.44	6.94	6.00	6.00	–	5.44	6.94

[a] Determined by GC/MS; ratio **3b'**/**3b''** is based on GC/MS of **2b'** and **2b''**; other isomers were determined only in traces.

reduction systems such as Zn/HCl, SnCl₂/HCl, Sn/HCl, LiAlH₄, and NaBH₄ were unsuitable as well since reaction did either not occur or yielded the corresponding diazo compounds. Herein, we used a strategy incorporating triiron dodecacarbonyl which is in situ converted to [Fe₃(CO)₁₂][–], a powerful reductant even under mild reaction conditions.^[13] Reactions were carried out in toluene/methanol^[14] or under organic/aqueous phase-transfer conditions in the presence of a strong base.^[15] The use of the two-phase system toluene/aqueous KOH and [18]crown-6 as phase-transfer catalyst led to a straightforward reduction of both **2a** and **2b**. In contrast to the reduction with triiron dodecacarbonyl in homogenous medium,^[13] this reaction system does not require heating under reflux. Quantitative reduction of **2a** and **2b** is achieved with stirring for 2 h at room temperature. No polymerization or degradation products of [2.2]paracyclophanes were found under these conditions. Compounds **3a** and **3b** were free of unreacted nitro or diazo compounds as determined by GC/MS, IR, and NMR studies.

The combination of nitration at low temperature in superacidic medium and reduction with [Fe₃(CO)₁₂][–] at room temperature provides an extremely mild pathway toward **3a**

and **3b**. Strict control of selectivity and milder reaction conditions allow the synthesis of **3a** and **3b** in overall yields as high as 90%. So far, the direct synthesis of **3b** from [2.2]paracyclophane as a two-step procedure was reported only in two cases.^[11, 16] Overall yields for the two-step procedure were either not reported or as low as 4% to 7%.^[17]

CVD polymerization of **3a** resulted in transparent polymer films of poly(amino-*para*-xylylene-co-*para*-xylylene) (**4**). The polymer coating shows excellent adhesion on the copper substrates used in this study. Polymer **4** is insoluble in all common solvents. Its elemental composition was determined by X-ray photoelectron spectroscopy (XPS) to be in accordance with the theoretical composition. The IR spectrum of polymer **4** confirmed the presence of primary amino groups as indicated by characteristic signals at wavelengths of 3359 and 3431 cm^{–1}. These free amino groups provide anchor groups for further functionalization. The feasibility of using polymer **4** as functionalized interface for biomedical applications was recently proven by the immobilization of a thrombin inhibitor on metallic cardiovascular implants.^[18]

Experimental Section

2a: Acidic ion exchange resin (Nafion) (15.44 g) was incubated in argon atmosphere with nitric acid (100%; 5 mL) for 12 h and subsequently rinsed five times with dichloromethane. [2.2]Paracyclophane (420 mg, 2 mmol) dissolved in dichloromethane (50 mL) was added to a suspension of the superacidic resin in dichloromethane (50 mL). After the mixture had been stirred for 90 min at 0 °C and 60 min at 24 °C, the suspension was quenched with ice water, extracted with diethyl ether, and purified by column chromatography to give **2a** in 95% yield. ¹H NMR (300 MHz, CDCl₃, TMS): δ = 2.88–3.30 (7H, CH₂), 4.10 (1H), 6.63–6.95 (4H, CH), 7.23–7.33 (3H, CH); ¹³C NMR (75 MHz, CDCl₃, TMS): δ = 33.54, 34.27, 34.66, 35.34, 126.31, 127.98, 129.21, 135.51, 136.55, 137.18, 137.38, 137.69, 141.68, 142.02, 142.39, 149.83; IR (KBr): $\tilde{\nu}$ = 868 (CN), 1196 (NO₂), 1519 (NO₂), 2938 (CH) cm^{–1}; MS (70 eV): *m/z*: 253 [*M*⁺], 104 [main, C₈H₈⁺], 91 [C₇H₇⁺], 78 [C₆H₆⁺], 65 [C₅H₅⁺].

2b: Nitric acid (100%; 0.8 mL) was added at room temperature to a solution of trifluoromethanesulfonic acid (3.5 mL) in dichloromethane (30 mL). After stirring for 15 min under an argon atmosphere, the solution was cooled to –78 °C and a solution of [2.2]paracyclophane (2 g, 9.6 mmol) in dichloromethane (80 mL) was added slowly. The solution was stirred for 20 min at –78 °C and another 120 min at –20 °C. Quenching with ice water, extraction with diethyl ether, and subsequent column chromatography delivered **2b** in 93% yield. ¹H NMR (300 MHz, CDCl₃, TMS): δ = 2.88–3.30 (7H, CH₂), 4.10 (1H), 6.63–6.95 (3H, CH), 7.23–7.33 (3H, CH); ¹³C NMR (75 MHz, CDCl₃, TMS): δ = 33.54, 34.27, 34.66, 35.34, 126.31, 127.98, 129.21, 135.51, 136.55, 137.18, 137.38, 137.69, 141.68, 142.02, 142.39, 149.83; IR (KBr): $\tilde{\nu}$ = 868 (CN), 1196 (NO₂), 1519 (NO₂), 2938 (CH) cm^{–1}; MS (70 eV): *m/z*: 298 [*M*⁺], 149 [C₈H₇–NO₂⁺], 133 [C₈H₇–NO⁺], 103 [C₈H₇⁺], 91 [main, C₇H₇⁺], 77 [C₆H₅⁺], 65 [C₅H₅⁺].

3a: 4-Nitro[2.2]paracyclophane (2 g, 6.67 mmol), triiron dodecacarbonyl (1.12 g, 6.67 mmol) and [18]crown-6 ether (90 mg) were dissolved in toluene (200 mL). Subsequently, 1N KOH (200 mL) were added and the solution was stirred for 2 h at room temperature. Extraction with diethyl ether and subsequent column chromatography delivered **3a** in 95% yield. ¹H NMR (300 MHz, CDCl₃, TMS): δ = 2.54–2.62 (1H, CH₂), 2.64–3.08 (7H, CH₂), 3.36 (2H, NH₂), for aromatic protons see Table 1; ¹³C NMR (75 MHz, CDCl₃, TMS): δ = 32.23, 33.03, 34.95, 35.37, 122.36, 122.99, 124.60, 126.82, 131.48, 132.43, 133.23, 133.44, 138.91, 138.97, 141.06, 144.72; IR (KBr): $\tilde{\nu}$ = 722, 800, 1287, 1425, 1509, 1562, 1620, 2857, 2928, 3002, 3032, 3061, 3383, 3474 cm^{–1}; MS (70 eV): *m/z*: 223 [*M*⁺], 119 [main, C₈H₇NH₂⁺], 104 [C₈H₈⁺], 91 [C₇H₇⁺], 78 [C₆H₆⁺], 65 [C₅H₅⁺].

3b: Dinitro[2.2]paracyclophane (2 g, 6.67 mmol), triiron dodecacarbonyl (2.24 g, 13.23 mmol), and [18]crown-6 ether (176 mg) were allowed to react and worked-up as described for **3a**. ¹H NMR (300 MHz, CDCl₃, TMS): δ =

2.54–2.62 (1H, CH₂), 2.64–3.05 (6H, CH₂), 3.08–3.19 (1H, CH₂), 3.36 (4H, NH₂), for aromatic protons see Table 1; ¹³C NMR (75 MHz, CDCl₃, TMS): δ = 29.42, 31.48, 32.60, 34.55, 120.29, 120.46, 122.06, 122.26, 123.69, 123.83, 128.44, 133.76, 140.32, 140.36, 144.91, 145.45; IR (KBr): ν̄ = 675, 726, 803, 1429, 1509, 1562, 1620, 2857, 2928, 3002, 3222, 3336, 3360, 3430 cm⁻¹; MS (70 eV): m/z: 238 [M⁺], 119 [main, C₈H₇NH₂⁺], 91 [C₇H₇⁺], 77 [C₆H₅⁺], 65 [C₅H₅⁺].

4-Amino[2.2]paracyclophane (**3a**) was polymerized by using a self-designed CVD installation consisting of a sublimation zone, a pyrolysis zone, and a deposition chamber equipped with a sample holder.^[7] Compound **3a** (30 mg) was placed in the sublimation zone and a copper substrate was fixed on the sample holder being cooled to 8 °C. The pressure was adjusted to 0.1 mbar and the pyrolysis zone was heated to 750 °C. Subsequently, **3a** was sublimed slowly resulting in a transparent film of polymer **4** on the copper substrate. XPS (referenced to hydrocarbon at 285.0 eV): C_{1s}: 93.9% (calcd: 94.1%), N_{1s}: 6.1% (calcd: 5.9%) atom%; IR (grazing angle of 85°): ν̄ = 814, 865, 1155, 1286, 1424, 1516, 1583, 1618, 2863, 2946, 3012, 3047, 3359, 3431 cm⁻¹.

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Active-Site Structure and Dynamics of Cytochrome *c* Immobilized on Self-Assembled Monolayers—A Time-Resolved Surface Enhanced Resonance Raman Spectroscopic Study**

Daniel H. Murgida and Peter Hildebrandt*

Self-assembled monolayers (SAM) of alkanethiol derivatives on metal electrodes provide numerous possibilities for immobilizing redox proteins.^[1] In the past few years, such devices have gained increasing interest in (nano)biotechnology. In particular, the current and potential importance of immobilized enzymes for the design and development of biosensors,^[2] bioelectronic systems,^[3] or biocatalytic cells^[4] has stimulated a large number of experimental studies in this field. Customizing the catalytic functions and optimizing the efficiencies of these systems represent a challenge in current research as they require a detailed characterization of the structural and functional properties of the redox-active adlayers as well as of the dynamics of the processes involved. Such investigations impose high demands on the sensitivity and selectivity of the analytical tools. In most cases, microscopic and electrochemical methods such as atomic force microscopy and cyclic voltammetry (CV) are employed which, however, do not provide information about the molecular structure of the species involved in the redox process. In this respect, time-resolved surface-enhanced resonance Raman (TR-SERR) spectroscopy, which exclusively probes the vibrational spectra of the redox sites solely of the immobilized species, is a powerful alternative approach for analyzing molecular structure and dynamics of the adsorbed enzymes.^[5]

So far, TR-SERR spectroscopy was restricted to redox proteins immobilized on bare Ag electrodes which, however, do not represent systems of general biotechnological applicability due to potential denaturation of proteins directly adsorbed on the Ag surface. In this work, we have employed TR-SERR spectroscopy for the first time to probe the heterogeneous electron transfer (ET) process of a heme protein immobilized on a SAM-coated Ag electrode. As a test redox protein we chose cytochrome *c* (Cyt-*c*) which has been studied by various electrochemical techniques including CV, electrochemical impedance, and electroreflectance.^[6–8]

After electrochemical roughening of the Ag electrode,^[5] SAMs of 11-mercaptopundecanoic acid (11-MUDA; Aldrich) were prepared according to previously published procedures.^[9] For the adsorption of Cyt-*c*, the electrode was dipped in a solution containing 2 μM of the purified protein (horse heart, Sigma) as well as 12.5 mM KCl and 12.5 mM phosphate buffer (pH 7.0) for 30 min. Subsequently, this

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buffer was used for rinsing the electrode to remove unbound Cyt-*c* prior to inserting the electrode into the SERR cell containing a Cyt-*c*-free solution of the same electrolyte composition. SERR spectra were measured with 413-nm excitation using a home-built rotating Ag electrode to avoid laser-induced desorption and protein degradation.^[5b] TR-SERR measurements were carried out by probing the SERR spectra during the time intervals Δt (typically 500 μ s) after a delay time δ with respect to a potential jump from an initial potential E_i to a final potential E_f . The method and the experimental set-up are described in detail by Wackerbarth et al.^[5b, 10]

The intensity of the stationary SERR spectra of Cyt-*c* bound to the SAM-coated Ag electrode was found to be lower by not more than a factor of 2 compared to Cyt-*c* adsorbed on a bare Ag electrode. These findings, which are in line with previous observations,^[11, 12] imply that the distance-dependent attenuation of the surface enhancement still allows the measurement of high-quality SERR even at a separation of about 19 Å between Cyt-*c* and the electrode. During the experiments, the SERR intensity decreased by less than 10 %, indicating an efficient electrostatic binding of Cyt-*c* to the carboxylate groups of the SAM through the lysine-rich domain around the exposed heme edge of the protein.^[13] The analysis of the SERR spectra focused on the region between 1300 and 1700 cm^{-1} that includes the vibrational bands of the heme that are characteristic of the various oxidation, spin, and ligation states of Cyt-*c*.^[13] Hence, this spectral region is of particular importance for identifying Cyt-*c* species that exhibit different active site structures.^[5] Except for a slight broadening of the bands, the SERR spectra, measured at +0.05 and −0.4 V,^[14] are essentially identical to the respective resonance Raman (RR) spectra of oxidized and reduced Cyt-*c* in solution, implying that the structure of the heme pocket remains unchanged upon binding to SAMs of 11-MUDA. These findings are in contrast to those for Cyt-*c* adsorbed on a bare Ag electrode where electrostatic interactions induce a potential-dependent conformational equilibrium between the native form of Cyt-*c* (state B1) and a new state (state B2) that lacks the axial Met-80 ligand and exhibits a strong negative shift of the redox potential.^[5b, 13, 15] Thus, the analysis of the redox process of Cyt-*c* at the 11-MUDA-coated Ag electrode is substantially simplified such that only two spectrally different species have to be considered, that is, the reduced and the oxidized forms of Cyt-*c* in the (native) B1 state. Consequently, superpositions of the component spectra^[5] of these two species yield very good and unambiguous fits to all measured SERR spectra between +0.05 and −0.4 V so that the potential-dependence of the redox equilibrium could be determined with high accuracy. The Nernst plot yields an excellent linear correlation with a slope corresponding to $n=0.96$. The redox potential was determined to be −0.031 V which is about 40 mV more negative than the redox potential of Cyt-*c* in solution.^[16] This potential shift can be rationalized in terms of a potential drop at the redox site due to its separation from the electrode by the SAM.^[5c, 17]

TR-SERR experiments were carried out by applying potential jumps to the final potential of −0.031 V, that is,

the redox potential, by using delay times between 500 μ s and 40 ms. As an example, the TR-SERR spectrum measured at $\delta=8.5$ ms after a potential jump from $E_i=-0.074$ V to $E_f=-0.031$ V is displayed in Figure 1 along with the stationary SERR spectra measured at E_i and E_f . Also in the TR experiments, the SERR spectra reveal no contributions of Cyt-*c* species other than the native reduced and oxidized state B1 so that the component spectra of these two species allow a consistent fit to the experimental spectra on the entire time scale. Thus, the time-dependent concentration changes can be analyzed in terms of a one-step relaxation process that refers to the heterogeneous ET between the adsorbed Cyt-*c* and the Ag electrode. Indeed, a semilogarithmic plot of the deviations from the equilibrium concentrations as a function of δ yields a straight line with a very good correlation and an intercept close to the theoretical value of zero (Figure 2a). From the slope, the formal heterogeneous

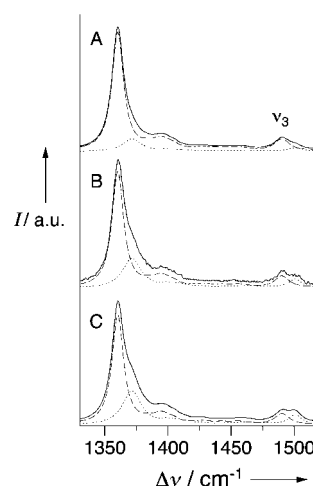


Figure 1. SERR spectra of Cyt-*c* adsorbed on an 11-MUDA-modified Ag electrode for a potential jump from $E_i = -0.074$ V to $E_f = -0.031$ V. Traces A) and C) are the stationary SERR spectra measured at E_i and E_f , respectively. Trace B) shows the TRSERR spectrum measured at 8.5 ms after the potential jump. The dashed and the dotted lines indicate the component spectra of the reduced and oxidized Cyt-*c*, respectively.

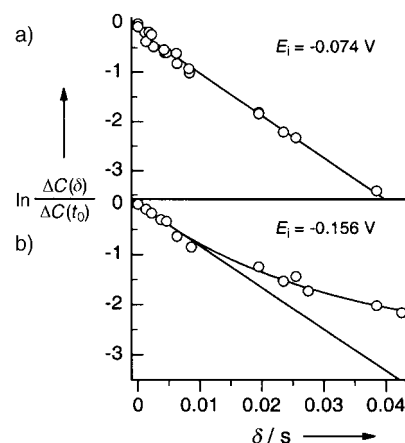


Figure 2. Semilogarithmic plot of the concentration changes of the reduced Cyt-*c* as a function of the delay time δ as determined by TR-SERR spectroscopy. $\Delta C(\delta)$ and $\Delta C(t_0)$ denote the deviations from equilibrium concentrations for $E_f = -0.031$ V at $t = \delta$ and $t = 0$, respectively. The upper diagram (a) refers to a potential jump from $E_i = -0.074$ V to $E_f = E^0$, the lower one (b) to a potential jump from $E_i = -0.156$ V to $E_f = E^0$.

rate constant (at $E_f = E^0$) is determined to be 43 s^{-1} , which is somewhat smaller than the values derived from electrochemical experiments at SAM-coated Au electrodes (60–72 s^{-1}) by electrochemical methods.^[6d, 8]

By applying larger potentials jumps from more negative initial potentials to $E_i = E^0$, the dynamics of the ET becomes more complex as shown in Figure 2b for $E_i = -0.156$ V. Whereas at delay times shorter than about 7 ms, the semi-logarithmical plot of the concentration changes reveals a linear behavior with the same slope as determined for $E_i = -0.074$ V (Figure 2a), at longer delay times substantial deviations from linearity are found.^[18] These deviations indicate that at large potential jumps a second and relatively slow non-Faradaic process interferes with the ET of the adsorbed Cyt-*c*. Since the analysis of SERR spectra and the ideal Nernst behavior rule out the involvement of conformational transitions that include changes of the heme pocket structure and, thus, alterations of the redox potential, it is concluded that there is a potential-dependent equilibrium between adsorbed Cyt-*c* species that solely differ by the ET kinetics. Such differences may result from different orientations of the heme with respect to the SAM which in turn may be brought about by electrostatic binding through different lysine residues in the binding domain of Cyt-*c*. Since this part of the protein surface includes about 10 lysine residues,^[19] variations of the heme orientations may easily be achieved without changing the distance of the redox center from the Ag electrode.^[20] Following this interpretation, it may be that at potentials close to E^0 , Cyt-*c* is predominantly bound through an orientation that enables a fast ET. Decreasing the potential may thermodynamically favor an orientation of the bound Cyt-*c* that is associated with a slower ET rate. Consequently, very negative values for E_i should lead to a substantial population of this latter species. Thus, the additional slow phase in the relaxation kinetics (Figure 2b) may either reflect directly the ET of this species or its reorientation followed by a fast ET. At small potential jumps, the equilibrium distributions among the different populations are likely to be similar at E_i and E^0 so that the relaxation process can adequately be approximated by a single exponential (Figure 2a).^[21, 22]

According to this interpretation, at potentials above E^0 essentially all the adsorbed Cyt-*c* molecules should be adsorbed in the orientation that is favorable for the ET. This conclusion is in fact confirmed by measurements with large potential jumps from $E_i = +0.1$ V to E^0 . In this case, the ET kinetics is monophasic with a rate constant of 39 s^{-1} that is nearly identical to that obtained for small potential jumps from negative potentials.

In contrast to TR-SERR spectroscopy, electroactive and -inactive species cannot be identified and distinguished by CV and its applicability for analyzing the ET kinetics of adsorbates is questionable or, at least, limited.^[23] However, a coupling of Faradaic and non-Faradaic processes may be indirectly reflected by electrochemical experiments. Thus, the peak broadening observed in cyclic voltammograms of Cyt-*c* on SAM-modified Au electrodes was attributed to a dispersion of kinetic or thermodynamic parameters of the redox process.^[6a-c] On the basis of the present TR-SERR results, the electronic coupling constant is suggested to be the crucial parameter as it should sensitively depend on the orientation of the adsorbed Cyt-*c* even though the possible orientations are not likely to be associated with different ET distances.^[20] On the other hand, distributions of reorganization energies or

redox potentials, as suggested previously by Bowden et al.,^[6b] can be ruled out since differences in these parameters should be sensitively reflected by differences in the redox site structures. However, the SERR spectra do not reveal any indication for such a structural heterogeneity of the bound Cyt-*c* (see above).

These results illustrate the principle advantages of TR-SERR spectroscopy, which is suitable for monitoring time-dependent processes of adsorbed redox proteins directly and selectively and simultaneously providing information about the active site structures of the various species involved. Thus, TR-SERR spectroscopy represents a powerful approach to analyze the dynamics and mechanism of complex interfacial processes of immobilized enzymes and promises to become an important analytical tool for investigating molecular structures and testing the performance of nanoscale devices in biotechnology.

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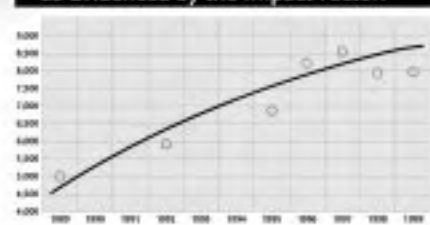


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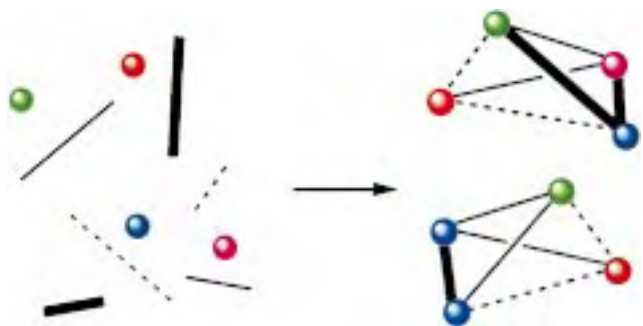
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Combinatorial Libraries of Metal–Ligand Assemblies with an Encapsulated Guest Molecule**

Marco Ziegler, J. J. Miranda, Ulla N. Andersen, Darren W. Johnson, Julie A. Leary, and Kenneth N. Raymond*

Remarkable self-assembled polyhedral structures of high symmetry are found in nature. In some cases, subunits are interchangeable and assemble in mixtures of different components to form a structure with higher functionality and complexity. For example, the multicatalytic protease complex in the archaebacterium *Thermoplasma acidophilum* consists of 14 identical protein subunits assembled in a cylindrical structure with D_7 symmetry,^[1] whereas the proteasome in a higher organism, the yeast *Saccharomyces cerevisiae*, is made of pairs of seven different protein subunits assembled in a structure with C_7 symmetry.^[2]

A number of synthetic coordination clusters of various sizes, stoichiometries, and symmetries has recently been described and reviewed.^[3–5] We have shown that careful consideration of the geometric requirements of a particular symmetry and stoichiometry for a cluster leads to the controlled formation of M_4L_4 (T),^[6] M_4L_6 (S_4 and T),^[7, 8] M_6L_6 (D_3),^[9] M_6L_8 (O), and M_8L_8 (D_{4d})^[10] assemblies (with point symmetry noted). By combination of different subunits out of a pool of available ligands and metals, a large array of different assemblies (a library) can be obtained. Here we report the formation of libraries of tetrahedral M_4L_6 complexes (Scheme 1) and describe the synthesis and character-



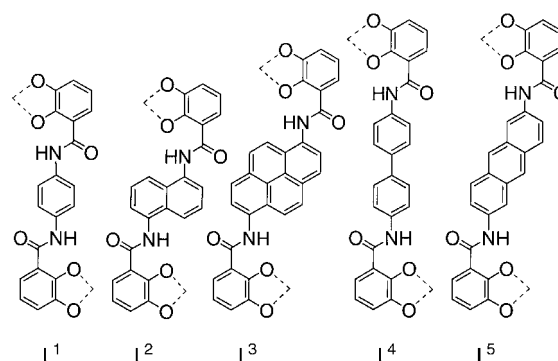
Scheme 1. A schematic representation of the generation of a supramolecular library consisting of 152496 possible tetrahedral M_4L_6 assemblies made from 10 different components with homoconfigurational metal centers.

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ization of such assemblies made of combinations of various biscatecholate ligands (Scheme 2).^[11] Each assembly is able to encapsulate a tetraalkylammonium cation as a guest in its cavity, as we have previously observed for the $Ga_4L_6^2$ coordination cluster.^[8]



Scheme 2. The biscatecholate ligands used in this study, which have varying linker units between the chelating groups.

The size of such a library increases rapidly with the number of different subunits used (Table 1). Including the possibility of having metal centers with Δ or Λ chirality, a total of

Table 1. Number of different ligand combinations and total number of diastereomeric species formed for a homochiral M_4L_6 assembly made of different ligands L .

Number of different ligands n	Number of ligand combinations	Total number of diastereomers
1	1	1
2	7	12
3	28	87
4	84	416
5	210	1475
6	462	4236

2488212 diastereomeric assemblies can theoretically be formed out of ten different subunits (six different ligands and four different metals) with a very broad probability distribution of species.^[12] Ligand arrangements and statistical weights have been derived by using a computer program.^[13]

We chose to start with the simplest case: a mixture of two different ligands (L^2 and L^3) and one metal cation (Ga^{III}). This gives rise to twelve diastereomeric assemblies with ligand arrangements shown in Figure 1. We found that many, if not all, possible combinations of ligands and different spatial arrangements of a given number of components are indeed present in solution, and that they do not interconvert on the NMR time scale. The individual components of the library were characterized by NMR spectroscopy (Figure 2a) and ESI-FTICR MS^[14] (Figure 3). The encapsulated guest molecule (Et_4N^+) is an ideal NMR probe to distinguish the different isomers formed since the large upfield shift of the proton resonances of Et_4N^+ , which is indicative of encapsulation,^[8] is strongly dependent on the number and spatial arrangement of aromatic rings present in the assembly. ESI has previously proven useful for characterizing multiply charged

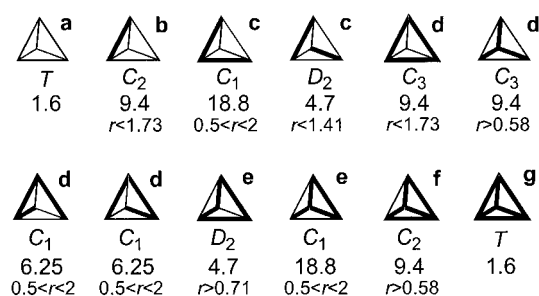


Figure 1. All possible arrangements (diastereomers) of two different ligands in a tetrahedral assembly with homoconfigurational metal centers. Isobaric species are labeled with the same letter. Underneath each species are noted 1) the point group symmetry, 2) the statistical weight (%) assuming a 1:1 ratio of ligands, and 3) the ratio r of lengths of the two ligands required to form the assembly.

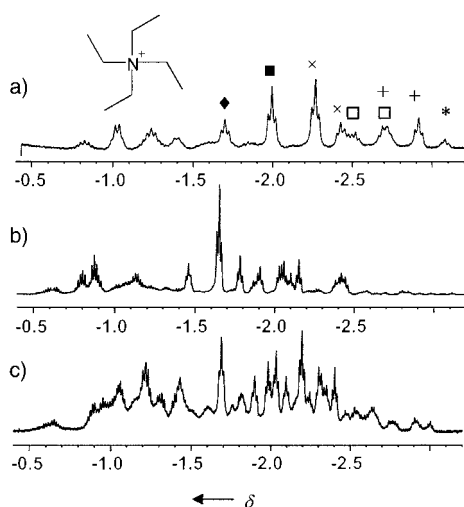


Figure 2. NMR spectra of encapsulated Et_4N^+ in libraries of $[\text{Ga}_4\text{L}_6 \supset \text{Et}_4\text{N}]^{11-}$ complexes. The methyl resonances of various species are marked and assigned as follows: a) $\text{L}^2/\text{L}^3 = 2:1$ $\blacklozenge$ Ga_4L_6^2 ; $\blacksquare$ $\text{Ga}_4\text{L}_3^3\text{L}^3$; $\times$ $\text{Ga}_4\text{L}_4^3\text{L}^3$; $\square$ $\text{Ga}_4\text{L}_3^3\text{L}^3$ (four diastereomers); $+$ $\text{Ga}_4\text{L}_3^3\text{L}^3$ (two diastereomers); $*$ $\text{Ga}_4\text{L}_2^3\text{L}^3$ b) $\text{L}^1/\text{L}^2/\text{L}^3 = 1:4:1$, c) $\text{L}^1/\text{L}^2/\text{L}^3/\text{L}^4 = 1:4:1:1$.

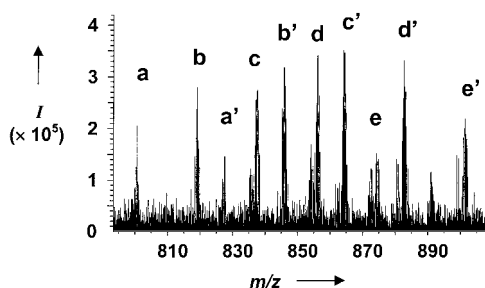


Figure 3. Electrospray ionization Fourier transform ion cyclotron resonance mass spectra (ESI-FTICR-MS) of a library formed with ligands L^2 and L^3 in 1:1 ratio: a) $[\text{Ga}_4\text{L}_2^3\text{L}_3^3 \supset (\text{Et}_4\text{N})]\text{Na}_7^{4-}$; b) $[\text{Ga}_4\text{L}_3^3\text{L}_4^3 \supset (\text{Et}_4\text{N})]\text{Na}_7^{4-}$; c) $[\text{Ga}_4\text{L}_3^3\text{L}_3^3 \supset (\text{Et}_4\text{N})]\text{Na}_7^{4-}$; d) $[\text{Ga}_4\text{L}_4^3\text{L}_3^3 \supset (\text{Et}_4\text{N})]\text{Na}_7^{4-}$; e) $[\text{Ga}_4\text{L}_3^3\text{L}^3 \supset (\text{Et}_4\text{N})]\text{Na}_7^{4-}$. In the species denoted with prime, a sodium cation is exchanged by Et_4N^+ . I = intensity in arbitrary units.

coordination compounds in solution.^[15, 16] FTICR detection allowed us, for the first time, to analyze libraries of such negatively charged supramolecules with very high resolution and mass accuracy.

The binary library described above represents the true thermodynamic equilibrium: while boiling for several days no

change in composition of the library was observed. Furthermore, when an aqueous solution of $[\text{Ga}_4\text{L}_6^2 \supset (\text{Et}_4\text{N})]^{11-}$ and another solution containing $[\text{Ga}_4\text{L}_6^3 \supset (\text{Et}_4\text{N})]^{11-}$ were mixed and heated for several hours at 60°C the very same library formed. Time-dependent NMR studies of L^1/L^2 , L^1/L^3 , and L^2/L^3 mixtures revealed the kinetics of this process. The assignment of NMR peaks of newly appearing species was based on the assumption that ligands are exchanged stepwise and with equal probability for each ligand [Eqs. (1) and (2)].



We compared the actual concentration of species present with the concentration predicted by a first-order statistical model^[17] for the ligand-exchange process and found that the experimental data were in good agreement with such a model. Figure 4 shows the measured data for a L^2/L^3 mixture and the

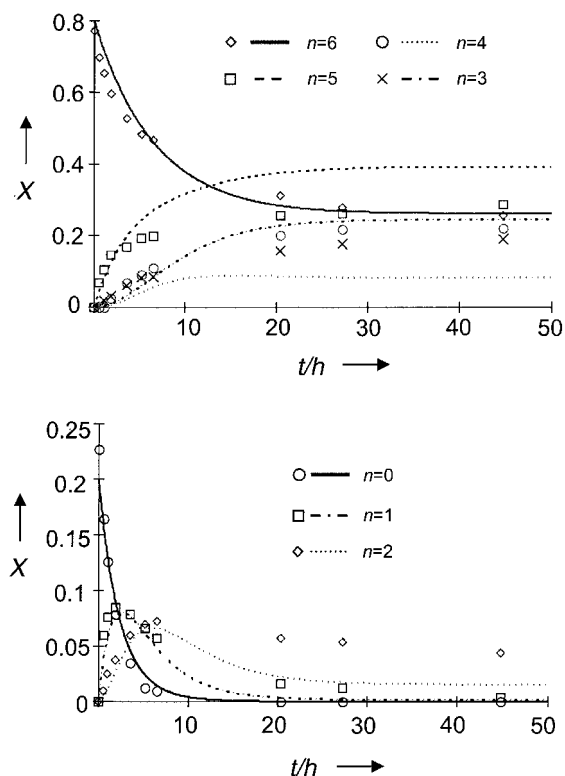


Figure 4. Time-dependent concentration of different species ($x=1$ mole fraction) $[\text{Ga}_4\text{L}_n^2\text{L}_{6-n}^3 \supset (\text{Et}_4\text{N})]^{11-}$ as determined by NMR spectroscopy (points) and calculated according to a statistical model (lines) from a mixture containing pure $[\text{Ga}_4\text{L}_6^2 \supset (\text{Et}_4\text{N})]^{11-}$ and $[\text{Ga}_4\text{L}_6^3 \supset (\text{Et}_4\text{N})]^{11-}$ in a 4:1 ratio initially (D_2O solution at pD 7.5 at 60°C).

calculated values according to the model with $k=1.5(3) \times 10^{-4} \text{ s}^{-1}$ (60°C in D_2O solution, pD 7.5). Similar rates of $0.8(2) \times 10^{-4} \text{ s}^{-1}$ and $0.6(3) \times 10^{-4} \text{ s}^{-1}$ were obtained for the ligand-exchange process of L^1/L^2 and L^1/L^3 mixtures, respectively.

Mixtures of ligands L^1/L^2 , L^1/L^3 , L^2/L^4 , and L^3/L^4 formed very similar libraries. The ligands L^1 and L^4 incorporate into a tetrahedral assembly even though $[\text{Ga}_4\text{L}_6^1 \supset (\text{Et}_4\text{N})]^{11-}$ or

$[\text{Ga}_4\text{L}_6^4 \supset (\text{Et}_4\text{N})]^{11-}$ are not observed; these ligands prefer to form the corresponding entropically favored $[\text{Ga}_2\text{L}_3]^{6-}$ assemblies.^[18] Interestingly, a library made of ligands L^2 and L^5 was kinetically stable at room temperature for several weeks, but thermodynamically unstable forming pure $[\text{Ga}_4\text{L}_6^2 \supset (\text{Et}_4\text{N})]^{11-}$ and $[\text{Ga}_4\text{L}_6^5 \supset (\text{Et}_4\text{N})]^{11-}$ complexes upon boiling in water or DMSO for several hours.

Using a mixture of ligands L^1 , L^2 , and L^3 , 28 possible combinations of ligands and a total of 87 diastereomers can be formed (Table 1). NMR spectra show that a wide distribution of species is indeed obtained (Figure 2b), however, the complexity and number of isomers present does not allow unambiguous assignment of NMR peaks of the structures present. Figure 5 shows the mass spectral data of a library

Table 2. Statistically most abundant and experimentally observed masses in a single run of a 1:4:1 mixture of ligands L^1 , L^2 , and L^3 forming a library of $[\text{Ga}_4\text{L}_x^1\text{L}_y^2\text{L}_z^3 \supset (\text{Et}_4\text{N})]^{11-}$ complexes. All other possible species have calculated probabilities lower than 3% and have not been observed in the ESIMS spectra.

<i>x</i>	<i>y</i>	<i>z</i>	Probability [%]	Peaks assigned (Figure 5)
2	4	0	8.2	A
1	5	0	13.2	B (B' with Na^+ exchanged by H^+)
2	3	1	8.2	C
0	6	0	8.8	D
1	4	1	13.2	E
0	5	1	13.2	F
1	3	2	8.2	G
0	4	2	8.2	not observed

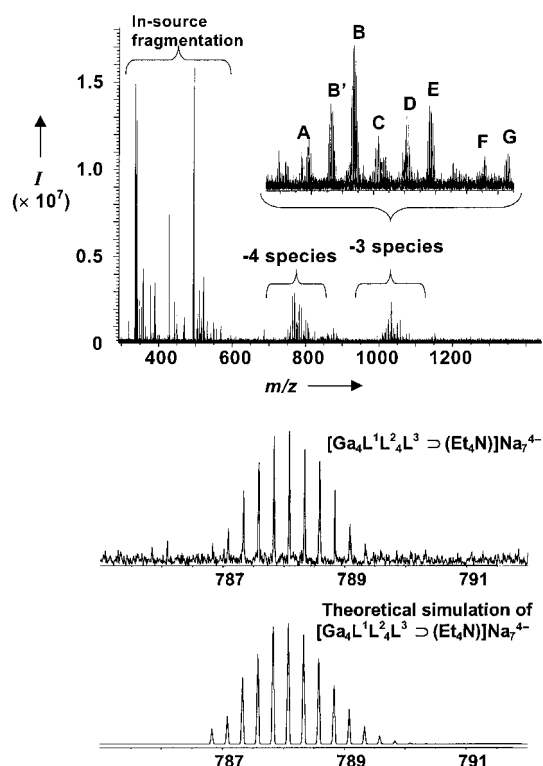


Figure 5. ESI-MS spectra of various $[\text{Ga}_4\text{L}_x^1\text{L}_y^2\text{L}_z^3 \supset (\text{Et}_4\text{N})]\text{Na}_{12}$ species where the ligands were mixed in the following initial ratio: $\text{L}^1:\text{L}^2:\text{L}^3 = 1:4:1$ (assignment according to Table 2).

containing metal complexes of the composition $[\text{Ga}_4\text{L}_x^1\text{L}_y^2\text{L}_z^3 \supset (\text{Et}_4\text{N})]^{11-}$. The statistically most probable combinations for *x*, *y*, and *z* (Table 2) are observed.^[19] A mass scale expanded segment (Figure 5) shows the spectrum of the $[\text{Ga}_4\text{L}_1^1\text{L}_4^2\text{L}_3^3 \supset (\text{Et}_4\text{N})]\text{Na}_7^{4-}$ species, which deviates less than 10 ppm from the calculated isotope distribution. Since all combinations of ligands differ in their masses, the high resolution and high mass accuracy of the FTICR instrument makes it uniquely possible to assign the peaks in the spectrum and consequently provide exact information about the elemental composition of the ion cluster in question. Mixtures of four (Figure 2c) or more ligands gave libraries with a very large number of species, which we have not yet been able to fully characterize. Given research in the area of ESI of metal–ligand complexes which shows com-

parability between solid-, solution-, and gas-phase structures,^[20–24] there is a precedent for the data described here. We find both stereochemical differentiation and metal-coordinated dendrimer composition in the gas phase that reflects the solution conformation as well as mass spectral data of single crystals which again reflect the isolated and purified product. Retention of solution-phase structure has been shown for metal ion bipyridine complexes^[23] and various metal macrocycle complexes.^[24] An error of 10 ppm for the mass spectral data is in excellent agreement with theory and although attachment of alkali metal ions is observed in the gas phase, there has been no evidence of ligand clustering. When combined with the NMR data, the overall structure, coordination number, and composition of the complexes are reliably determined.

A statistical distribution of compounds is also obtained when different metal cations, such as mixtures of $\text{In}^{\text{III}}/\text{Ga}^{\text{III}}$ are used with the same ligand. Given the similarity in size and charge of the metals used, this is anticipated, but it underlines again the principle of obtaining a mixture of self-assembled compounds containing all possible combinations of subunits.

The term “virtual” dynamic combinatorial library^[25] has been proposed for the formation of labile assemblies where out of many possible (virtual) structures only certain species form, which is the foundation for recognition associated with self-assembly processes. We demonstrate here that a “real” supramolecular dynamic combinatorial library with many assemblies simultaneously being present in solution is made from labile ligands and metals forming kinetically inert assemblies with an encapsulated guest molecule. The investigation of the kinetics and thermodynamics of self-assembly processes involving different subunits reveals insight into how diversity and complexity in molecular assemblies is achieved. We are currently investigating such libraries for screening of supramolecular hosts encapsulating small molecules.

Experimental Section

All NMR spectra were measured with a Bruker 500-MHz spectrometer. Chemical shifts are reported as in ppm downfield from tetramethylsilane (TMS). Mass spectral data were acquired using a Bruker ApexII 7 Tesla actively shielded FTICR mass spectrometer equipped with an Analytica electrospray source (off axis probe). Sample solutions were $300 \text{ pmol } \mu\text{L}^{-1}$ in methanol with Na^+ as counterions. Hexapole storage time: 0.5 s; capillary exit voltage: 100 V.

Bis(bidentate) catecholamide ligands (Scheme 2) were synthesized according to previously published procedures.^[20] Libraries were obtained following a simple procedure: H_4-L^2 (33.1 mg, 0.077 mmol), H_4-L^3 (39.0 mg, 0.077 mmol), Et_4NCl (4.3 mg, 0.026 mmol), and $[Ga(acac)_3]$ (acac = acetylacetonate) (37.1 mg, 0.102 mmol) were suspended in methanol (20 mL). A 0.5 N NaOH solution (620 μ L) in H_2O was added slowly, and a clear solution was obtained. After the mixture had been stirred for 2 h, the solvent was reduced to 4 mL, and excess acetone was added to precipitate the product, which was collected by ultracentrifugation, washed with acetone and dried (quantitative yields). The same library was obtained by mixing solutions of $[Ga_4L_6^2 \supset (Et_4N)]^{11-}$ and $[Ga_4L_6^3 \supset (Et_4N)]^{11-}$ at pD 7.5 after heating for several hours at 60 °C.

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- [12] Six ligands with four metals can give 16710 different arrangements for a total of 152496 diastereomers. If the possibility of heteroconfigurational metal centers is considered, 2488212 possible diastereomers can be formed: 152496 for $\Delta\Delta\Delta\Delta/\Delta\Delta\Delta\Delta$ (T), 840420 for $\Delta\Delta\Delta\Delta$ (S_4), and 1495296 for $\Delta\Delta\Delta\Delta/\Delta\Delta\Delta\Delta$ (C_3). With six different ligands in equimolar amounts and one metal cation, 4236 homoconfigurational diastereomers can be formed, out of which 3590 each has a probability of 0.02572 % to form, 540 form with a probability of 0.01286 %, and all others (106) have an abundance of 0.006 % or below. For the $\Delta\Delta\Delta\Delta$ assemblies, out of 12006 possible diastereomers, 11340 (94.5 %) have a probability (0.0086 %) to be formed; for the $\Delta\Delta\Delta\Delta$ assemblies, out of 15576 diastereomers, 15540 have an abundance of 0.00643 % each.
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$$\frac{d}{dt}[A_6] = k \left[-b[A_6] + \frac{1}{6}a[A_5B] \right] \quad (3)$$

$$\frac{d}{dt}[A_5B] = k \left[\frac{1}{3}a[A_4B_2] + b[A_6] - \left(\frac{5}{6}b + \frac{1}{6}a \right) [A_5B] \right] \quad (4)$$

$$\frac{d}{dt}[A_3B_3] = k \left[\frac{2}{3}a[A_2B_4] + \frac{2}{3}b[A_4B_2] - \left(\frac{1}{2}b + \frac{1}{2}a \right) [A_3B_3] \right] \quad (5)$$

$$\frac{d}{dt}[A_4B_2] = k \left[\frac{5}{6}a[A_3B_3] + \frac{1}{2}b[A_3B_3] - \left(\frac{1}{3}b + \frac{2}{3}a \right) [A_4B_2] \right] \quad (6)$$

$$\frac{d}{dt}[AB_5] = k \left[a[B_6] + \frac{1}{3}b[A_2B_4] - \left(\frac{1}{6}b + \frac{1}{6}a \right) [AB_5] \right] \quad (7)$$

$$\frac{d}{dt}[B_6] = k \left[-a[B_6] + \frac{1}{6}b[AB_5] \right] \quad (8)$$

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Shape Selectivity in Hydrocarbon Conversion**

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Molecular sieves with three-dimensional framework structures find many applications in catalysis.^[1, 2] A comprehensive and fundamental understanding of the product selectivity associated with these catalytic processes remains a formidable challenge of considerable practical significance.^[3] Herein we focus on conversion reactions of alkanes. We demonstrate that molecular sieves favor the formation of reaction intermediates that have a shape commensurate with their pore shape.

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The ultimate fate of these intermediates depends on whether diffusion, hydrocracking, or methyl shifts have the lowest Gibbs free energy barrier. We obtain microscopic information on the adsorbed molecules using configurational-bias Monte Carlo simulations. This information on a molecular level enables the explanation of peculiarities in known product distributions.^[4–6]

The conversion of linear alkanes can be described as a series of consecutive reactions each increasing the degree of branching (monobranched, dibranched, etc.).^[7] Methyl shifts can transfer these molecules into isomers with the same number of branches. Together with this increasing degree of branching, consecutive hydroisomerization reactions increasingly compete with hydrocracking reactions that decompose the molecule. The overall mechanism is therefore a very complex scheme with many different reaction intermediates.^[8] The products of the reaction are a mixture of the various isomers and their hydrocracking products and can be seen as a fingerprint of the molecular sieve.

To arrive at a general mechanism that can explain the shape-selective conversion of alkanes we assume that the Polanyi–Brønsted principle holds. This principle implies that equilibrium thermodynamics reflect the relative probability of formation of a particular isomer, provided it is formed through the same reaction mechanism as other, competing isomers.^[9, 10] Whether this isomer will appear in the product distribution depends on the relative rates of diffusion and of consecutive reactions (hydrocracking or hydroisomerization). Since isomers with the branches at the same carbon atom or at carbon atoms one methylene (CH_2) group apart undergo hydrocracking three orders of magnitude faster than the other isomers,^[8] we assume that hydrocracking occurs only through these isomers.

Differences in the Gibbs free energy of formation determine the equilibrium concentration of the various reaction intermediates. If we use the tabulated free energies of formation in the gas phase,^[11] we would predict that all routes contribute comparably to the overall conversion and that all branched isomers will form. In fact, such a product distribution is observed in the FAU-type zeolite, which indicates that this large-pore zeolite does not modify the thermodynamic product distribution.^[7, 8] However, by using gas-phase thermodynamics, we implicitly assume that the change in Gibbs free energy for the transfer of a molecule from the gas phase into the sieve

is similar for all reaction intermediates. For the large FAU-type pores^[12] this is a reasonable assumption, but not for zeolites with smaller pores. Since the contribution of the sieve to the free energies of formation cannot always be obtained from available experimental data, we use configurational-bias Monte Carlo (CBMC) simulations^[13a] to compute the contribution of the zeolites to the free energies of formation.

Figure 1 shows the contribution of several zeolites to the Gibbs free energy of formation of the various reaction intermediates involved in decane conversion. The differences between the various isomers in the gas phase are relatively small (5 kJ mol^{-1} at most).^[11] Similar differences are found in the FAU-type zeolite. Large differences in the Gibbs free energy between the various intermediates are observed in MFI-, MEL-, and TON-type zeolites. For example, the Gibbs free energy of formation of the tri-branched alkanes with proximate methyl groups is very large. The formation of these isomers will therefore be suppressed.^[9, 10] In this way the Gibbs free energy modifications afford an unambiguous assessment of the possibility for shape selectivity of the transition state. Experimentally, such an assessment has often proved to be difficult.^[3]

To investigate the mobility of a reaction intermediate we have computed the Gibbs free energy of this molecule as a function of its position in the sieve.^[14] If this Gibbs free energy profile shows barriers that are much larger than the thermal energy ($\gg 1k_{\text{B}}T$), diffusion will be slowed down by the zeolite. In MEL- and MFI-type zeolites, mono-methyl alkanes have a

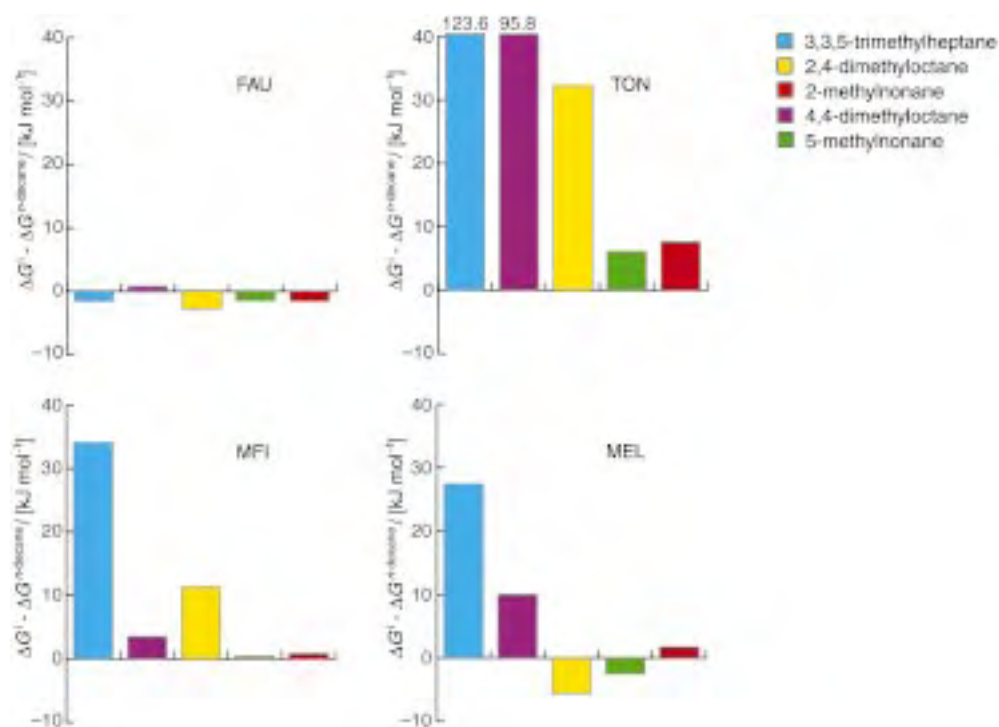


Figure 1. The Gibbs free energy of formation of hydrocarbons relative to decane in FAU-, TON-, MFI-, and MEL-type sieves as obtained from CBMC simulations.^[13b] The interaction parameters used in this study can reproduce the experimental adsorption isotherms of linear and branched alkanes in various zeolites accurately.^[13a] The changes in the Gibbs free energy were calculated using one molecule at infinite dilution at $T = 415 \text{ K}$. At this temperature the Gibbs free energy of formation of all C_{10} isomers in the gas phase is $(149 \pm 2) \text{ kJ mol}^{-1}$. Only the isomers with the greatest influence on the product distribution are shown. Details on the technique and the model can be found in Vlucht et al.^[13a]

barrier of $12\text{--}14k_{\text{B}}T$, while in TON-type zeolites it is only $6k_{\text{B}}T$. These values indicate that diffusion rates of mono-methyl alkanes are lower in MEL- or MFI-type zeolites than in TON-type zeolites. Quantitatively similar results were obtained from molecular dynamics simulations.^[15, 16] The Gibbs free energy profiles of some di-branched isomers in MEL and MFI are compared in Figure 2. These results indicate that the dimethylalkanes have a barrier of $15\text{--}60k_{\text{B}}T$, which results in diffusion coefficients ranging from 10^{-16} to $10^{-32}\text{ m}^2\text{ s}^{-1}$. These diffusion coefficients are too low to be calculated by molecular dynamics simulations.^[15, 16]

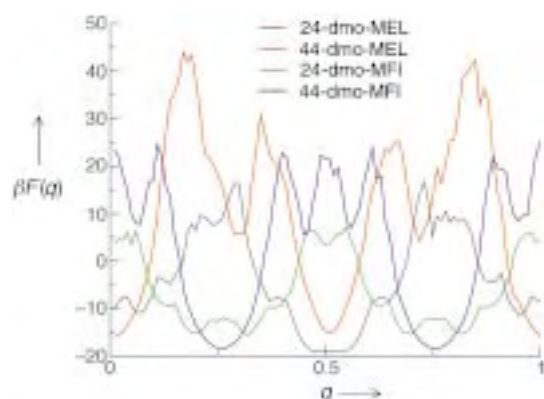


Figure 2. Gibbs free energy (in units of $k_{\text{B}}T$) as a function of the position of the n,m -dimethyloctane (dmo) isomers in MEL- and MFI-type zeolites. We have limited the calculation to the straight channel for MFI-type zeolites; similar results are obtained for a zigzag channel. Instead of calculating the average Gibbs free energy of a molecule in a zeolite (as is done in Figure 1), we compute the Gibbs free energy as a function of the position of the molecule along a channel. The parameter q is the fractional coordinate with respect to the unit cell of the 3-position of the chain in the case of 2,4-dmo and the 4-position in case of 4,4-dmo. The middle of the intersections in a MEL-type zeolite have reduced coordinates of $q = 0.25$ and $q = 0.75$ and in an MFI-type zeolite of $q = 0$, $q = 0.5$, and $q = 1$. The reported diffusion coefficients have been calculated using these Gibbs free energy profiles assuming that transition-state theory holds.

An explanation for the high hydrocracking selectivity of MEL- and MFI-type zeolites relative to TON- or FAU-type zeolites is that the former selectively reduce the Gibbs free energy of formation of those dimethylalkanes that hydrocrack most easily. Dimethylalkanes with methyl groups attached to the same carbon atom or separated by one methylene (CH_2) group hydrocrack more quickly than other dimethylalkanes because they form both secondary and tertiary carbocation transition states instead of only secondary carbocation transition states.^[5, 7] The formation of these isomers is enhanced, because their shape is commensurate with that of the pore intersection: 4,4-dimethyloctane fits snugly when it has its octane backbone in the straight MFI-type channel and the two methyl groups in the zigzag channel; 2,4-dimethyloctane on the other hand has a perfect fit in the large MEL-type intersection because the distance between the two branches matches the distance between the two intersecting channels. Those intermediates that are commensurate with the zeolite structure are preferentially formed but cannot diffuse out of the zeolite without being hydrocracked. Since hydrocracking of 2,4-dimethyloctane yields isobutane, while hydrocracking

of 4,4-dimethyloctane yields *n*-butane,^[7] we now understand why the conversion of *n*-decane using MEL-type zeolites yields about twice as much isobutane as that using MFI-type zeolites.^[4, 5] In this case the thermodynamic and diffusion properties can only be calculated: the dimethyloctanes studied diffuse too slowly to be amenable to traditional adsorption experiments.

We can apply this procedure to determine general trends in a product distribution for other hydrocarbon conversion processes. The aim of dewaxing is to transfer long-chain hydrocarbons (waxes) into branched isomers. Hydrocracking is an undesirable side reaction that we would like to suppress as much as possible. Figure 1 shows that the dimethylalkanes that most easily hydrocrack (alkanes with proximate methyl groups) have a relatively high Gibbs free energy of formation in TON-type zeolites. Figure 3 shows that TON-type zeolites

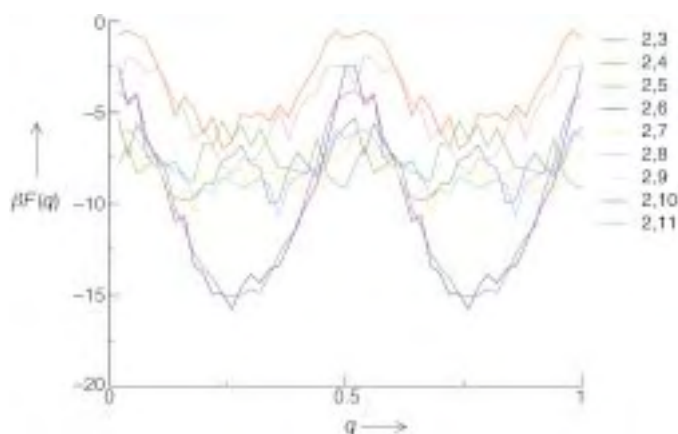


Figure 3. Gibbs free energy as a function of the position of the $2,m$ -dmpd isomers in TON-type zeolites (see also the caption to Figure 2).

instead favor the formation of di-branched alkanes with the methyl group separated by two or more methylene groups. 2,6- and 2,10-dimethylpentadecane (dmpd) have the lowest Gibbs free energy of formation. The shape of these two isomers is commensurate with the periodicity of the cavities in the TON-type zeolite channel (Figure 4). There is no such perfect match between the spacing of the methyl groups and that of the undulations in the TON-type channels for the other isomers. Figure 3 shows that commensurate 2,6- and 2,10-dmpd have a barrier of $15k_{\text{B}}T$, which gives a diffusion coefficient of $2 \times 10^{-13}\text{ m}^2\text{ s}^{-1}$, and shows that the diffusion of the incommensurate 2,7- or 2,9-dmpd is virtually unhampered. From this Figure we can deduce the Gibbs free energy of formation of the various $2,m$ isomers. The incommensurate isomers have similar Gibbs free energies while the commensurate 2,6-dmpd has a Gibbs free energy of formation $5k_{\text{B}}T$ lower. The barrier for all methyl shifts is only $1.5k_{\text{B}}T$ in the gas phase or in a wide-pore zeolite.^[8] The Polanyi–Brønsted principle suggests that TON-type zeolites raise this barrier (by some $5k_{\text{B}}T$) for the methyl shift of a commensurate isomer (2,6-dmpd) into an incommensurate one (2,5- or 2,7-dmpd), but leave the methyl shifts among incommensurate isomers unaffected. The reason for the relatively high barriers to diffusion of the commensurate intermediates is that the

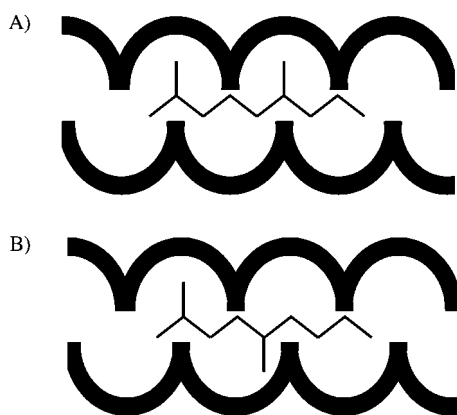


Figure 4. Sketch of a commensurate (A) and an incommensurate (B) molecule in a TON-type zeolite. If there are three carbon atoms separating the two methyl groups the molecule is commensurate with the zeolite structure. If we displace, for example, a 2,6-dimethylpentadecane (dmpd) isomer both methyl groups have to leave their optimal position. If we displace an incommensurate molecule, for example, the 2,5-dmpd isomer, part of the molecule always remains in an unfavorable configuration. As a consequence, the Gibbs free energy barriers of the incommensurate molecules are much smaller and hence these molecules diffuse faster.

diffusion of a commensurate isomer requires that both methyl groups leave their thermodynamically favorable sites, while the diffusion of an incommensurate molecule always involves one methyl group at an unfavorable position. Therefore a displacement of a commensurate molecule changes the Gibbs free energy more than that of an incommensurate molecule. A similar effect has been observed for clusters of molecules.^[17]

These simulation results lead to the following hydrocarbon conversion mechanism: The commensurate 2,6- and 2,10-dmpd will form preferentially but their barrier for diffusion is higher than their barrier for a methyl shift. Once a methyl shift has taken place, an incommensurate structure has formed which can leave the zeolite. However, 2,5-dmpd can easily undergo a methyl shift into 2,4-dmpd, which will hydrocrack before it leaves the zeolite. This suggests that in the product slate we may find some 2,5-, very little 2,6-, but a significant amount of 2,7-, 2,8-, and 2,9-dmpd isomers. Aspects of such a product distribution have been observed experimentally. Interestingly, these effects were explained in terms of catalysis at the *exterior* zeolite surface^[6] ("pore mouth" and "key lock" catalysis). Our interpretation implies catalysis inside the zeolitic pores. A similar conclusion has been obtained from molecular dynamics simulations.^[15, 16, 18] We have also calculated the Gibbs free energy profiles of the 3,*m*-dmpd isomers. For these isomers we find that 3,7-dmpd is the commensurate molecule. The Gibbs free energy of these 3,*m* isomers is $1-2k_B T$ higher than that of the 2,*m* isomers. We therefore expect that the product distribution also contains 3,8-, 3,9-, and 3,10-dmpd isomers in slightly smaller quantities.

It is instructive to compare our approach and the traditional concepts in shape-selective catalysis (reactant, transition state, and product shape selectivity^[3, 19, 20]). When a reactant is excluded from a zeolite (reactant selectivity), this is reflected by a very high Gibbs free energy of adsorption in our simulations.^[18] When the formation of a product or

intermediate is impeded or favored (transition state^[19] or inverse^[21] shape selectivity) the Gibbs free energy of such a molecule increases or decreases, respectively. When the diffusion rate of one product is slow relative to that of another (product shape selectivity^[20]) this shows up in the Gibbs free energy profile. Thus, CBMC calculations give a complete picture of shape selectivity, something that is very difficult experimentally.

An important concept in this work is whether a molecule is commensurate with the zeolite structure. The diffusion and thermodynamic characteristics of molecules whose shape is commensurate with that of the zeolite pore is very different from that of the incommensurate ones. These subtle differences have remarkably large influence on the product distribution.

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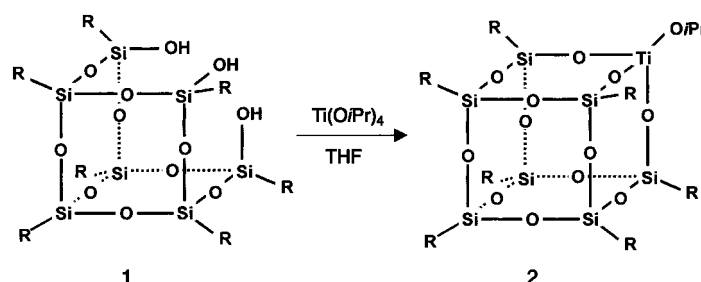
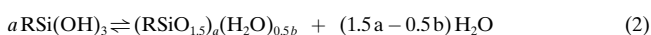
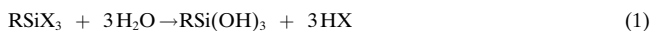
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A New, Efficient Route to Titanium–Silsesquioxane Epoxidation Catalysts Developed by Using High-Speed Experimentation Techniques**

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Titanium centers dispersed on, and supported by, various forms of silica are catalysts with remarkable properties for partial oxidations.^[1] The character of the active site varies with the silica support used. Although it has been established that in the best (on the basis of activity per gram of titanium) heterogeneous catalysts the Ti centers are all four-coordinate,^[2–4] it is still unclear whether, for optimum performance, the active catalytic species requires the specific configuration of four siloxy groups, or if being partially hydrolyzed to, say, one hydroxy and three siloxy ligands is equally good. Chemical modeling studies by various groups^[5–7] have shown that Ti catalysts with fewer than four siloxy groups should also be active as catalysts. These considerations indicate that there is still some residual uncertainty regarding the active site, despite the many experimental and computational studies carried out to resolve it.^[8, 9] Indeed, several mechanisms, or variations of one underlying mechanism, might operate depending on the precise configuration of the Ti site. Hence, different types of Ti centers might exhibit the desired characteristics.

For these catalysts, which are difficult to characterize, organic–inorganic hybrid compounds have proved to be useful models. Especially silsesquioxanes^[10–12] (RSiO_{1.5})_a·(H₂O)_{0.5b} (R is an organic group; *a* ≥ 1, *b* ≥ 0) have been a focus of attention as model compounds for silica. Of interest for catalysis are those silsesquioxanes that contain Si–OH groups, that is partially condensed structures to which a catalytically active compound can be complexed.^[13, 14] The incompletely condensed silsesquioxane trisilanol **1** (*a* = 7, *b* = 3) has recently been reported as a precursor for the soluble, titanium model compound **2** (Scheme 1), which results in an active catalyst for the epoxidation of alkenes.^[5–7] Silsesquioxane **1** can be obtained by the slow hydrolytic condensation of the corresponding monosilane RSiX₃ [Eq. (1) and (2); R = organic group; X = Cl, OMe, OEt; *a* + *b* = 2*n*; *n* = 1, 2, 3, ...;



Scheme 1. Complexation of titanium to the incompletely condensed silsesquioxane R₇Si₇O₁₂H₃ (R = cyclohexyl, cyclopentyl), modeling the grafting of titanium on silica.

b ≤ 3*a*).^[15] Besides compound **1**, the reaction may produce other silsesquioxane structures, some of which may also contain silanol groups that could react with titanium species to produce catalytic materials.

The preparation of compound **1** is time-consuming and requires a number of purification steps.^[15] Here we describe the application of high-speed experimentation techniques^[16] to optimize the preparation of silsesquioxanes as precursors for Ti catalysts active in the epoxidation of alkenes with peroxides. The aim is to identify a faster and cheaper way to synthesize silsesquioxane precursors for Ti catalysts. Since silsesquioxanes other than **1** may also show relevant catalytic activity after reaction with titanium, the synthesis of the silsesquioxane precursors was optimized not as a function of the yield in compound **1**, but rather as a function of the product yield due to the catalytic activity of the Ti silsesquioxanes in the epoxidation of 1-octene. The observed activity is thus the combined activity of all these compounds (vide infra).

Different factors may influence the reaction equilibria that determine which silsesquioxane structures and in what amounts are produced by the hydrolytic condensation of the organosilane RSiX₃.^[10, 12] Among those factors, the solvent and the nature of the organic group R are known to play a predominant role. Both the solvent and the R group influence the kinetic rate constant and the solubility of intermediates and products. The R group also affects the thermodynamic stability of the different silsesquioxane structures.

A number of solvents and trichlorosilanes were varied systematically to investigate a wide range of parameters. The chosen solvents are water-miscible, polar solvents: acetone, acetonitrile, methanol, and tetrahydrofuran (THF). The selected trichlorosilanes RSiCl₃ were either those usually employed (R = cyclohexyl and cyclopentyl) or those for which the corresponding open silsesquioxane **1** has not yet been reported in the literature (R = phenyl, methyl, *n*-octyl, allyl) but which were readily available.

In the preparation of the silsesquioxane-based catalysts, two general types of behavior regarding the solvents and the organotrichlorosilanes can be identified:

a) Catalysts derived from silsesquioxane structures that were synthesized in acetonitrile show the highest catalytic activity, followed, in decreasing order of activity, by those from acetone, methanol, and tetrahydrofuran (Figure 1 A). Interestingly, acetonitrile is more effective than acetone, the

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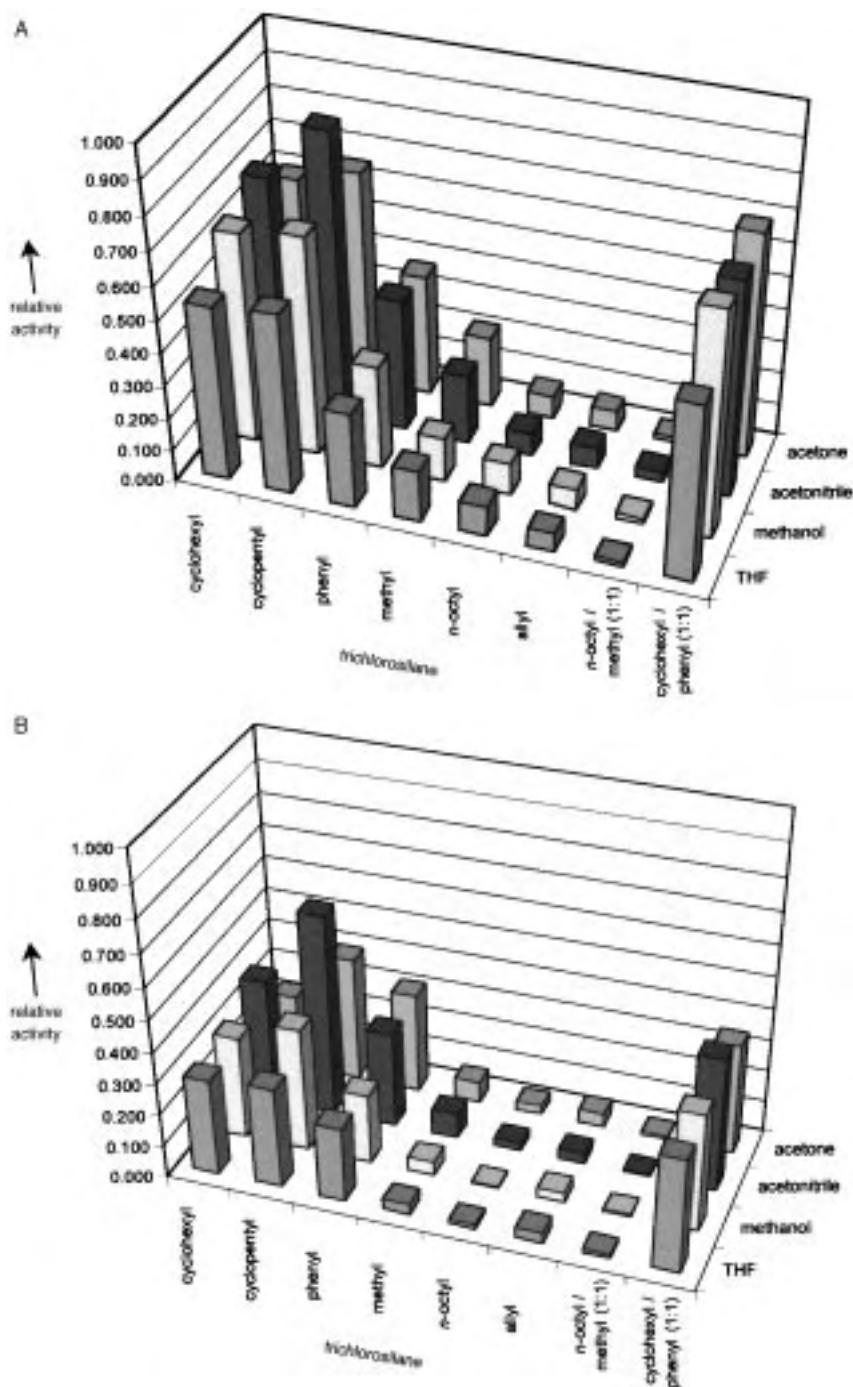


Figure 1. Activities of Ti-silsesquioxane catalysts (obtained by combining different trichlorosilanes and solvents, using water (A) or a 0.3 M HCl solution (B) as hydrolyzing agent) relative to Ti-cyclopentylsilsesquioxane catalyst **2** (activity set at 1) in the epoxidation of 1-octene.

solvent commonly reported for the synthesis of incompletely condensed silsesquioxane **1**.^[15] This result can be explained in terms of electric properties: amongst the solvents used, acetonitrile has the highest dipole moment and dielectric constant. Therefore, it can stabilize silsesquioxane species containing Si-OH groups, favoring their synthesis over that of the less polar, completely condensed silsesquioxanes.

b) With respect to the silanes employed, the highest epoxidation activities were observed in the order cyclopentyl > cyclohexyl > phenyl > methyl > allyl ~ *n*-octyl ~ 0,

regardless of the solvent used during the synthesis (Figure 1 A). This trend is in good agreement with the literature, where cyclopentyl- and cyclohexyltrichlorosilanes are reported to form incompletely condensed silsesquioxanes in high yields.^[15] In principle, the nature of the organic group might influence which silsesquioxane structures are produced and in which ratios,^[10] as well as the electronic and spatial properties of the actual catalyst. Considering that the organic groups are linked to the titanium center through a Si-O unit, electronic effects should have a negligible influence on the catalytic properties and, since the organic groups point away from the titanium center, steric effects are probably also not relevant. The principal effect of the organic group is, therefore, considered to be its role in determining which silsesquioxane structures are formed during the hydrolytic condensation and in which amounts.

The trend in the catalytic activity, as a function of the solvent used in the hydrolytic condensation, is not influenced by the nature of the organic group R. The activity trend as a function of the organic group is likewise not affected by the solvent. Therefore, regarding these trends, the solvent and organic group can be considered as independent variables.

The activities of the catalysts synthesized using high-speed experimentation techniques were compared with those of Ti(O*i*Pr)₄ and of the Ti-cyclopentylsilsesquioxane catalyst **2** produced by the reaction of pure cyclopentylsilsesquioxane **1** with Ti(O*i*Pr)₄. The high-speed experimentation catalysts with R = cyclohexyl, cyclopentyl, phenyl, and methyl show an activity higher than Ti(O*i*Pr)₄, confirming the formation of Ti-silsesquioxanes as the active species. Among these catalysts, the one derived from the combination of cyclopentyltrichlorosilane and acetonitrile displays the highest catalytic activity for the epoxidation of 1-octene (Figure 1 A). This activity is 87% of that of the Ti-cyclopentylsilsesquioxane catalyst **2**. The relevance of this result lies in the fact that the synthesis of our silsesquioxane precursors does not require any purification process and is much less time-consuming than the synthesis of compound **1**. Scaling up of the experiment to 100-mL scale yielded a catalyst with an identical activity, thus demonstrating that the small-scale high-speed experiment is comparable to conventional experimentation.

Two 1:1 molar mixtures of *n*-octyl- and methyltrichlorosilane and of cyclohexyl- and phenyltrichlorosilane were used to investigate possible synergetic effects between two differ-

ent organotrichlorosilanes in the formation of incompletely condensed structures (Figure 1A). The *n*-octyl/methyl mixture gave a very low epoxidation activity. As in the case of the pure *n*-octyl compound, the hydrolytic condensation produced a gel, generated by micelle formation due, probably, to the slower hydrolysis rate of long-chain alkylsilanes.^[12] Water retained in this gel would be inimical to the Ti insertion. The cyclohexyl-/phenyltrichlorosilane mixture showed considerable activity, suggesting the possibility of synergy between trichlorosilanes with different organic R groups.

Trying to further optimize the reaction, we investigated a variation of the ternary composition of the three most active silanes (cyclopentyl, cyclohexyl, and phenyl) in the best solvent (acetonitrile) (Figure 2). Although the highest epoxidation activity was found for the pure cyclopentyltrichlorosilane (i.e. the experiment did not lead to the identification of

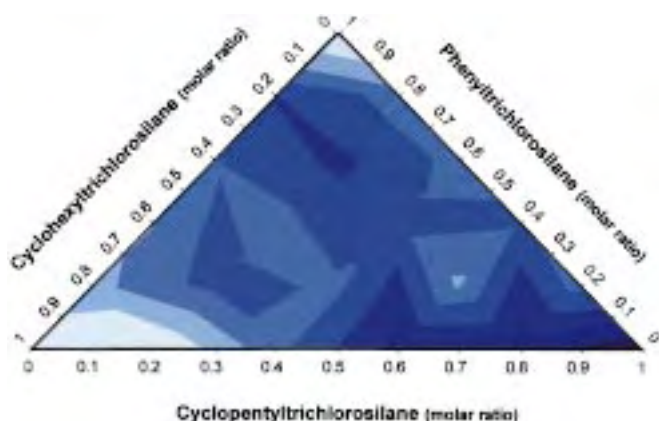


Figure 2. Activity in the epoxidation of 1-octene as a function of the ratio of cyclopentyl-, cyclohexyl- and phenyltrichlorosilanes in the initial silsesquioxane synthesis mixture (darkness of color $\propto$ activity).

a more active catalyst), the surface of the activity diagram shows some interesting features, underpinning the utility of the experiment: various mixtures yield catalysts with higher activities than those from pure cyclohexyl- and phenyltrichlorosilanes. Such behavior would have been difficult to identify without a combinatorial approach.

During the hydrolysis of the trichlorosilanes, hydrochloric acid is produced [Eq. (1)], which could influence the amounts of silsesquioxanes generated.^[10] To check this potential pH effect, the experiment was performed by using either H₂O or a 0.3 M HCl/water solution to hydrolyze the silanes. The trends observed with both are very similar (Figure 1) and a higher activity is found when using a neutral water solution (70% greater on average); thus extra hydrochloric acid is not beneficial.

We have shown that high-speed experimentation can be a valuable technique in the optimization of catalysts. A very active silsesquioxane-based catalyst for the epoxidation of 1-octene (cyclopentyltrichlorosilane hydrolyzed in acetonitrile) has been prepared by a much faster and cheaper method than conventionally possible. In addition to identifying the optimal synthesis conditions within the screened parameters, the large number of experiments performed by using high-speed experimentation techniques enabled us to gain addi-

tional insight in the system under study. Some general trends with respect to the roles of both the solvent and the organotrichlorosilane have been identified, and it has been shown that the synthesis of silsesquioxane catalysts is favored using a neutral rather than an acidified (HCl) solution. In future experiments, we plan to identify the most active Ti-silsesquioxane by a deconvolution of the complex silsesquioxane mixture. Moreover, we aim to use high-speed experimentation for further optimization of the synthesis of the silsesquioxane precursors, for the optimization of the Ti-insertion step, and for the introduction of aqueous hydrogen peroxide as oxidant.

Experimental Section

Experiments were performed on a parallel synthesis workstation^[17] by using four different solvents (acetone, acetonitrile, methanol, and tetrahydrofuran) and different silanes RSiCl₃ (R = cyclohexyl, cyclopentyl, phenyl, methyl, *n*-octyl, allyl, and mixtures of these). In a typical experiment, 6 × 2 mL aliquots of each of the four solvents were dispensed in a rack containing 4 mL glass tubes, followed by the addition of 340 μ mol of each of the six silanes to the solvent-containing reaction vessels in such a way that 24 individually different silane solutions were prepared. Hydrolysis of the silane was initiated by the addition of 0.5 mL of either water or a 0.3 M HCl solution to the reaction vessel and placing the vessel array on an orbital shaker at 50 °C for 18 h. After removal of the solvent and of the excess water and hydrochloric acid in a vacuum centrifuge, the samples were stored under argon. Titanium insertion was performed by dissolving the crude silsesquioxane mixture in THF (2 mL) under argon, followed by the addition of titanium isopropoxide. After 5 h at 50 °C, the tetrahydrofuran was removed by means of the vacuum centrifuge and the samples were stored under argon.

The catalytic activity of the materials obtained was determined by the epoxidation of 1-octene with *tert*-butyl hydroperoxide (TBHP). The reaction was performed by adding to each dried sample a solution of TBHP (~0.36 mmol) in cyclohexane (TBHP:catalyst ratio = 7.5) and 1-octene (0.0144 mol), which acted both as reactant and solvent (1-octene:catalyst ratio = 300). Prior to dispensing, 2 mL of decane was added for each 98 mL of 1-octene to serve as an internal standard in the following GC analysis. Samples were taken after the reaction had been allowed to proceed for 5 h at 60 °C and were analyzed on a UNICAM Pro GC using a CP-Sil-5B column. The epoxidation reaction proceeded very slowly at room temperature for several days; thus, the yield increased until a plateau was reached. The reported activities^[18] were obtained by normalizing the GC peak area for 1,2-epoxyoctane by means of the internal standard. Since the experiments were performed in 1-octene also as a solvent, it has not been possible to realize a mass balance. The reaction was completely selective in the synthesis of 1,2-epoxyoctane: no other products were detected. The conversion selectivity of TBHP towards 1,2-epoxyoctane lies between 80 and 94%.

The other catalysts (Ti(O*i*Pr)₄ and Ti-silsesquioxane **2**) were tested by using the same amount of titanium and the same experimental conditions as described above.

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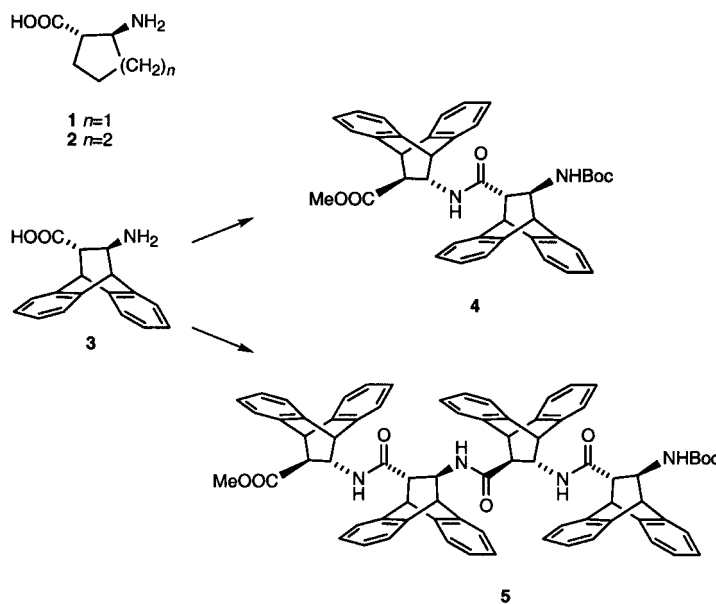
Design and Synthesis of Foldamers Based on an Anthracene Diels–Alder Adduct**

Jeffrey D. Winkler,* Evgueni L. Piatnitski, John Mehlmann, Jiri Kaspárec, and Paul H. Axelsen*

Dedicated to Professor Ronald Breslow on the occasion of his 70th birthday

The design and synthesis of peptides and peptide analogues with predictable and reproducible folding patterns is an

important goal.^[1] β -peptides are resistant to cleavage by most proteases and are therefore of considerable interest as building blocks in drug design.^[2] The groups of Seebach, Gellman, and DeGrado have demonstrated that oligomers derived from β -amino acids such as **1** and **2** can adopt predictable conformations that are a direct consequence of the nature of the monomeric building blocks **1** and **2** (Scheme 1).^[3] We reasoned that incorporation of two aromatic rings into **2** would constrain the amino acid backbone of oligomeric derivatives, creating foldamers with novel and well-defined hydrogen-bonding patterns.



Scheme 1.

We describe herein the preparation of the protected β -amino acid **9** from **6** (Scheme 2), the Diels–Alder adduct of anthracene and dimethyl fumarate, and the synthesis and study of both the dipeptide **4** and the tetrapeptide **5**. The presence of the dihydroanthracene moieties leads to a high level of structural definition in both **4** and **5**. The structure of **4** exhibits a unique level of organization. The NMR-derived solution structure of **5** reveals a twelve-membered ring helical conformation with a molecular volume of about 1200 Å³.

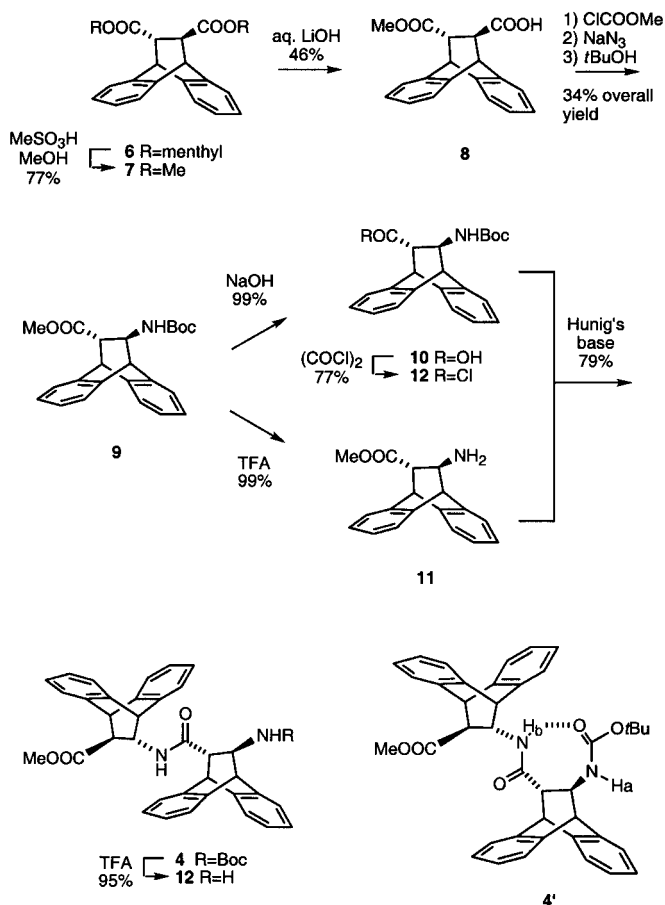
The synthesis of the tetracyclic β -amino acid monomer is outlined in Scheme 2. Reaction of anthracene with dimethyl fumarate under Lewis acid catalysis leads to the formation of **6** in 88 % yield and 99 % ee.^[4] Conversion of **6** to the corresponding dimethyl ester **7**^[5] in acidic methanol^[6] followed by saponification of **7** under mild basic conditions produces a statistical mixture of the desired monoacid **8**, along with the starting diester **7** and the corresponding diacid (not shown) which can be efficiently recycled. Curtius reaction of the acyl azide derived from **8** gave the *N*-Boc amino ester **9** in 34 % yield over three steps. Reaction of **9** with NaOH gave the corresponding acid **10**, whereas exposure of **9** to trifluoroacetic acid led to the formation of the deprotected amino ester **11**. Condensation of **12**, the acid chloride derived from **10**, with **11** gave dipeptide **4** in 79 % overall yield from **9**.

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Supporting information for this article (synthetic procedures and spectroscopic data for dipeptide **4**, tetrapeptide **5**, and all synthetic intermediates) is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 2.

The consequences of the introduction of the aromatic rings are exemplified by the unique structure of the resulting dipeptide **4**. Energy minimization of **4** leads to the eight-membered hydrogen-bonded ring structure **4'**, which can also be clearly identified in solution by ¹H NMR spectroscopy. The chemical shift of one of the N–H protons (H_a; δ = 4.4) in the ¹H NMR spectrum of dipeptide **4** is similar to the N–H resonance in the monomer **9** (δ = 4.5). However, the other N–H proton (H_b; δ = 7.5) in **4** is shifted downfield by 2 ppm relative to the chemical shift for H_b (δ = 5.5) that is observed for the amide proton in the free amine **12**. Deuterium-exchange experiments with **4** revealed that the upfield carbamate proton (H_a) undergoes rapid exchange (*t*_{1/2} = 20 min) in deuterated methanol, while the downfield amide N–H resonance (H_b) disappears slowly (*t*_{1/2} > 5 h; Figure 1). In contrast, rapid exchange of H_b is observed on exposure of free amine **12** to the same experimental conditions. These data support a pronounced difference in conformation between **4** and **12** which is consistent with the eight-membered ring hydrogen bonding shown in **4'**. This structural feature has been described by Yang and co-workers in α-aminoxy acids but is without precedent in β-amino acids.^[7] Well-defined secondary structure was observed in the systems derived from **1** and **2** only with tetra-β-peptide and larger systems.^[3a] A unique feature of this work and an important consequence of the presence of the dihydroanthracene moieties is that the secondary structure of dipeptide **4** is well-defined.

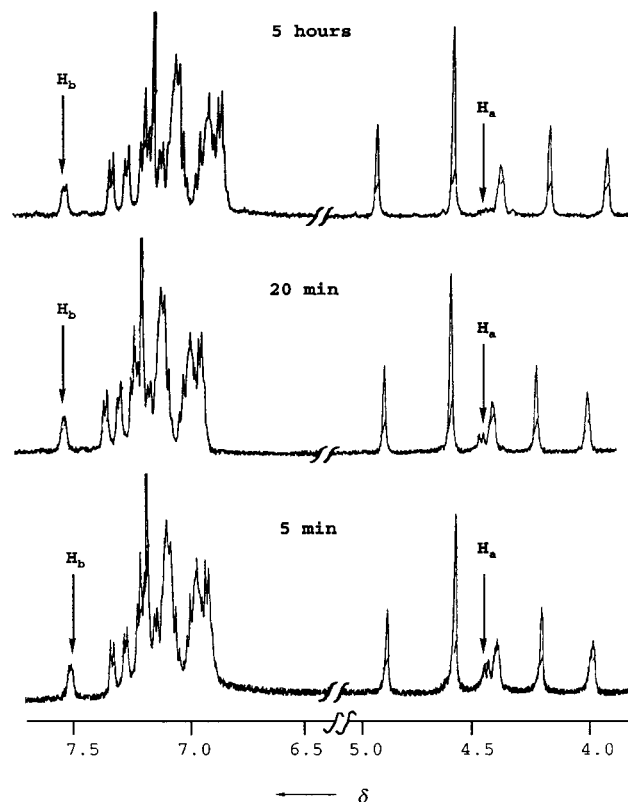


Figure 1. Deuterium (CD₃OD) exchange experiment with dipeptide **4** in CDCl₃.

We next examined the structure of the tetrameric product **5**, which was prepared by the same methodology used for the preparation of **4**. Reaction of the acid chloride derived from **4** with Hunig's base and the free amine derived from **4** gave the tetrameric product **5** in 66% overall yield from **4**. Careful examination of the ¹H NMR spectrum of **5** indicated the significant downfield shift of two of the four N–H resonances. Removal of the Boc group from tetrapeptide **5** led to a single downfield shift in the ¹H NMR spectrum of the derived amine, indicating that the Boc moiety is involved in hydrogen bonding in **5**. While peak overlap in the ¹H NMR spectrum of **5** did not allow deuterium-exchange experiments, the same information could be obtained from FT-IR spectra. As indicated in Figure 2, both hydrogen-bonded and non-hydrogen bonded amide N–H bonds can be detected in the dipeptide **4** and the tetrapeptide **5**, but not in the monomeric protected aminoester **9**.

Complete assignment of the ¹H NMR spectrum of the peptide backbone of **5** could be achieved by a combination of double quantum-filtered COSY^[8] and rotating-frame nuclear Overhauser effect spectroscopy (ROESY)^[9] and the identification of a series of long-range NOEs (see Supporting Information). The structure of **5** was then examined in energy-minimized structures sampled from an NOE-restrained molecular dynamics simulation performed at 300 K using CHARMM.^[10] These structures consistently exhibited a full 12-helical turn of the type illustrated in Figure 3. Both the eight- and twelve-membered hydrogen-bonded rings of **5** are shown explicitly in Figure 3a, and the peptide backbone of **5** is highlighted in Figure 3b.

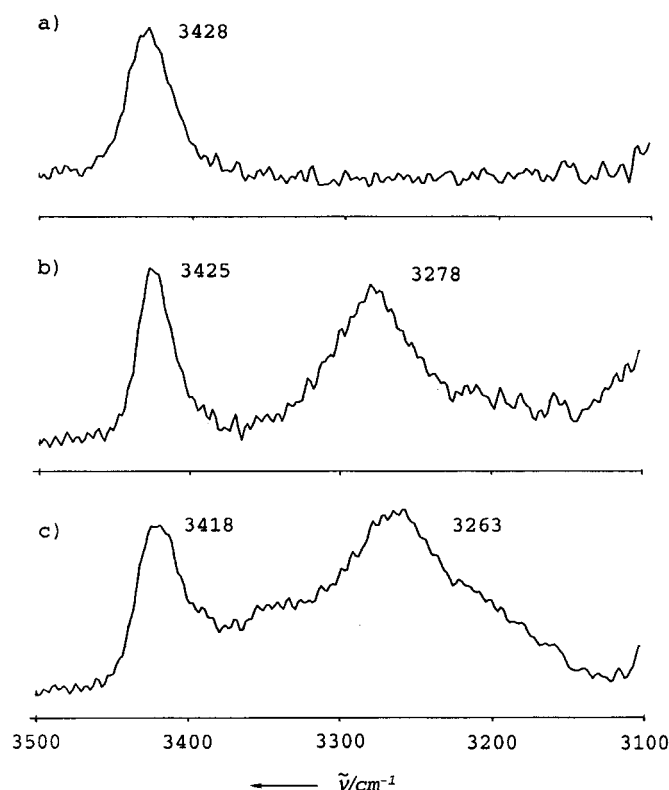


Figure 2. Amide N–H regions of IR spectra for *N*-Boc amino ester **9** (monomer), dipeptide **4**, and tetrapeptide **5**.

These results establish that high levels of conformational definition are observed in foldamers **4** and **5** derived from the anthracene Diels–Alder adduct **3**. The eight-membered hydrogen-bonded ring observed with **4** and the twelve-membered hydrogen-bonded ring and resulting helical structure in **5** illustrate the structural consequences of the incorporation of the novel β -amino acid **3**. Further studies on the effects of aryl substitution on these novel structures as well as the development of water-soluble systems are currently underway and our results will be reported in due course.

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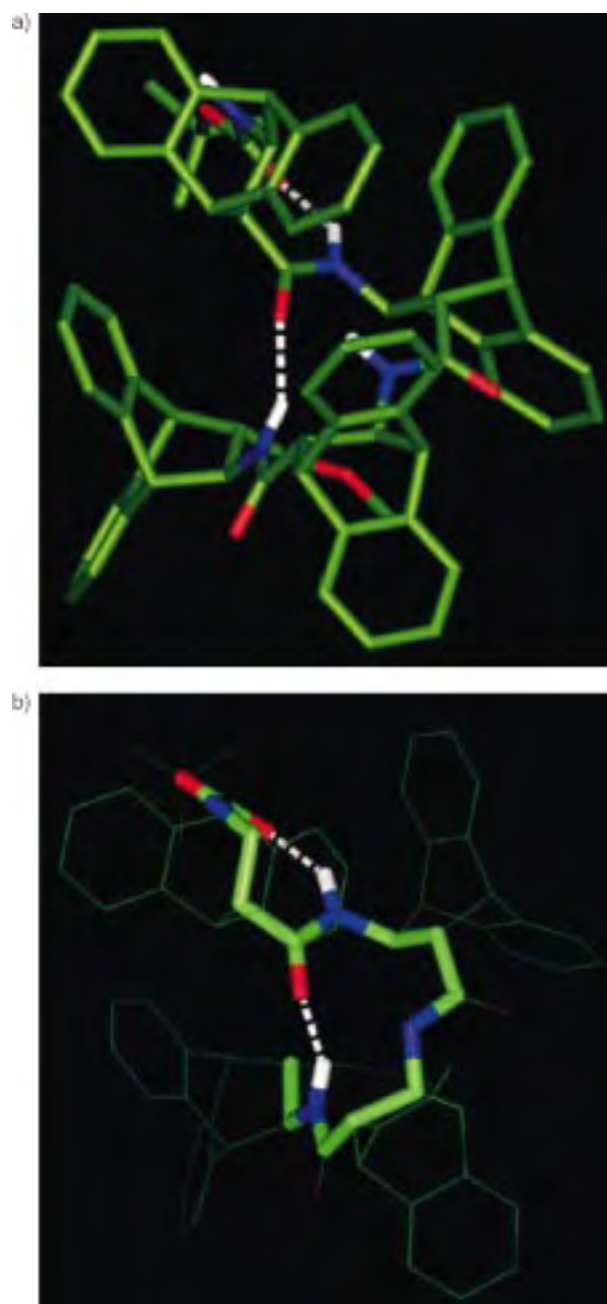


Figure 3. Solution structure of tetrapeptide **5**: a) full structure; b) peptide backbone.

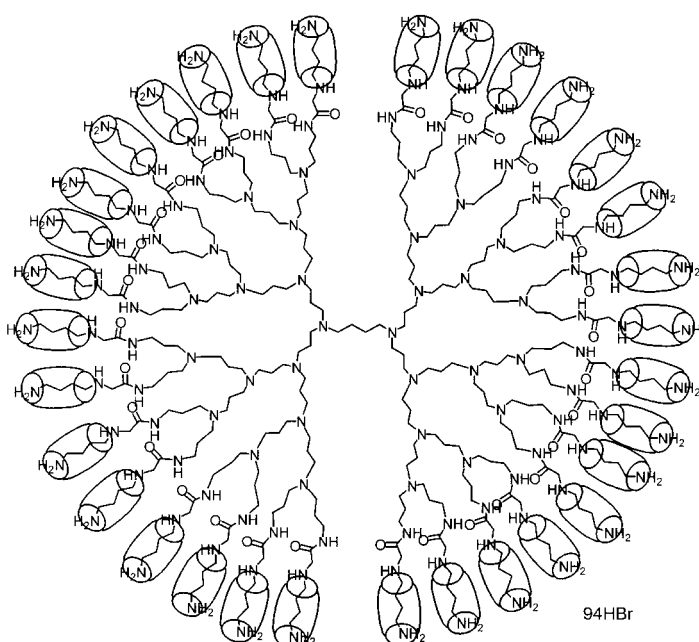
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Novel Pseudorotaxane-Terminated Dendrimers: Supramolecular Modification of Dendrimer Periphery**

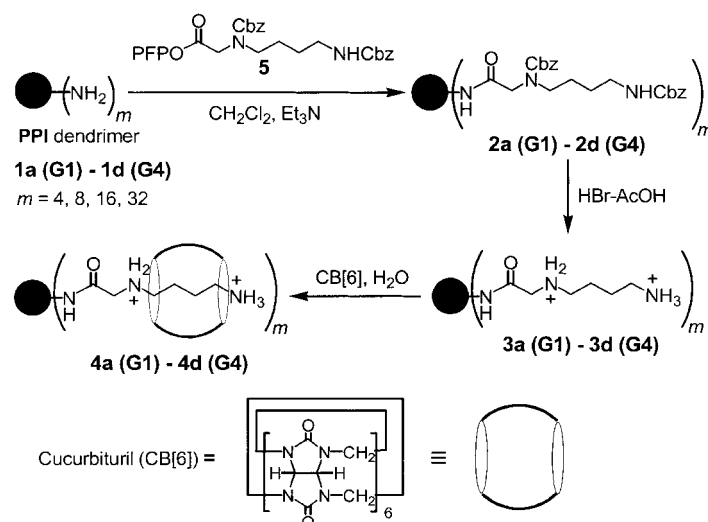
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The chemistry of dendrimers is blossoming into an exciting field of research. A wide variety of dendrimers with different cores, branches, and end groups have been synthesized and applied in different areas, such as in drug delivery, catalysis, light-energy harvesting, and sensors, during the past decade.^[1] Since many of the applications exploit functional groups at the periphery, the modification of terminal groups of dendrimers is of enormous current interest.^[2] Most of these modifications are achieved through formation of a covalent bond to the terminal groups. However, modifications using noncovalent bonds/interactions^[3] are more attractive as they offer many advantages, including reversibility. In fact, noncovalent bonds/interactions have been widely exploited in the self-assembly of supramolecular interlocked structures such as rotaxanes and catenanes.^[4] Our interest in interlocked structures led us to develop a simple and efficient method to synthesize polyrotaxanes and molecular necklaces.^[5] A key to the success of this method is to use cucurbituril (CB[6])^[6, 7] as a molecular “bead” which has an ability to form remarkably stable pseudorotaxanes with “strings” derived from diaminoalkanes through multiple noncovalent interactions. Encouraged by this success, we decided to explore the formation of pseudorotaxanes at the termini of dendrimers with the aim of providing an interesting way of modifying the dendrimer exterior by noncovalent interaction. Herein we report the formation of novel pseudorotaxane-terminated dendrimers and their characteristics (Scheme 1).^[8]

The synthesis of pseudorotaxane-terminated dendrimers **4a**(G1)–**d**(G4) is achieved in three steps (Scheme 2). Reaction of commercially available poly(propyleneimine) (PPI) dendrimers **1a**(G1)–**d**(G4) with **5**, which is easily synthesized from mono-Cbz-protected diaminobutane,^[9] followed by column chromatography affords dendrimers **2a**(G1)–**d**(G4), respectively, in good yield. The deprotection of the diaminobutane units in dendrimers **2a**–**d** with HBr–AcOH produces dendrimers **3a**(G1)–**d**(G4) containing protonated diaminobutane units at the termini. Treating **3a**–**d** with CB[6] affords



Scheme 1. Pseudorotaxane-terminated dendrimer **4d** (G4).



Scheme 2. Synthesis of pseudorotaxane-terminated dendrimers **4a**(G1)–**d**(G4). All the internal imine nitrogen atoms of **3** and **4** are also protonated. Abbreviations: PFP = pentafluorophenyl; Cbz = benzyloxycarbonyl.

the target pseudorotaxane-terminated dendrimers **4a**(G1)–**d**(G4). The number of molecular beads bound in **4** is 4, 8, 16, and 32 for **4a**–**4d**, respectively.

Figure 1 compares ¹H NMR spectra of the third generation dendrimers **3c** and **4c**. Note that the signals for the methylene groups (● and ▲) of the terminal diaminobutane units in **4c** which are located inside CB[6] are shifted upfield relative to those in **3c** while that of the methylene unit (*) adjacent to the carbonyl group in **4c** is shifted downfield. These observations are consistent with the structure of **4c** having pseudorotaxane units at the periphery of the dendrimers.^[6] A similar NMR spectral behavior is observed in other generation pseudorotaxane-terminated dendrimers **4**.

Electrospray ionization mass spectrometry was successfully employed in the characterization of **2** and **3**. The observed

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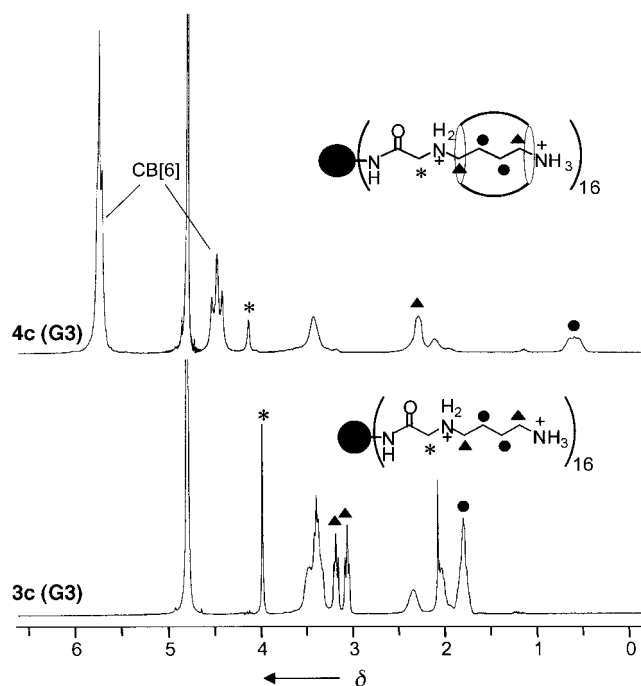


Figure 1. Comparison of the ^1H NMR spectra of the third-generation dendrimers **3c** and **4c**.

masses of the dendrimers are in excellent agreement with the calculated ones. The first-generation pseudorotaxane-terminated dendrimer **4a** also gave reasonable mass data.^[9] However, we failed to obtain decent mass spectra for the pseudorotaxane-terminated dendrimer of higher generations (**4b–d**). This result is presumably a consequence of the high molecular weights and charges of the pseudorotaxane-terminated dendrimers: for example, the third-generation dendrimer **4c** with 16 molecular beads (CB[6]) and 46 counterions (Br^-), which balance the 46 positive charges of the fully protonated dendrimer body, has a molecular weight of 23408 Da. Similar difficulty in characterization of dendrimers with high molecular weights and charges by mass spectrometry has been reported.^[2g, 10]

To understand the effect of threading CB[6] molecular beads onto the terminal groups of the dendrimer structures we decided to perform molecular dynamic (MD) simulation on the third-generation dendrimers **3c** and **4c**.^[11] Figure 2 shows typical conformations of these dendrimers obtained by MD simulation. The MD simulation results indicate that there is some backfolding of the terminal groups before the molecular beads are threaded onto them. Some aggregation of the terminal groups in each dendron is also observed. However, when CB[6] molecular beads are threaded onto the terminal groups they adopt a fully extended conformation and segregate from each other. This conformational change increases the overall size of the third-generation dendrimers from 40~41 Å (for **3c**) to 44~49 Å (for **4c**). These large terminal pseudorotaxane units appear to form a rigid shell at the exterior of the dendrimer, which may behave as a barrier isolating the inner space of the dendrimer from the bulk solvents.

The increased conformational rigidity arising from the threading of molecular beads at the dendrimer exterior has

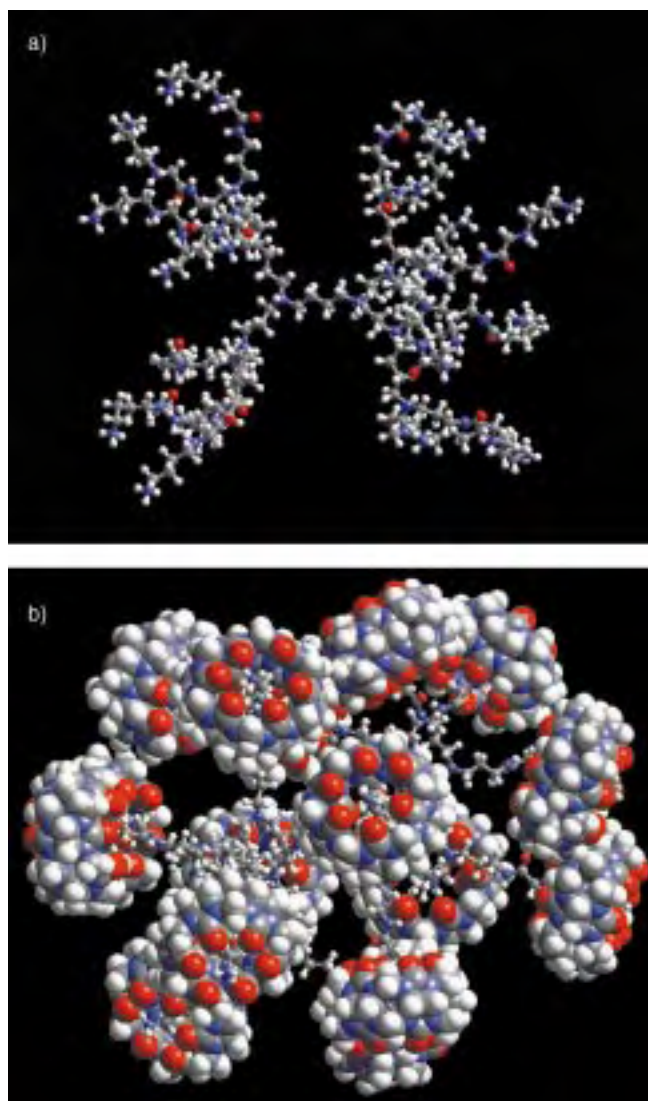


Figure 2. Structures of the third-generation dendrimers **3c** (a) and **4c** (b) obtained by MD simulation (after 520 ps). The dendrimer frameworks are represented with ball-and-stick models and the CB[6] molecular beads with a space-filling model. Color codes: oxygen: red; nitrogen: blue; carbon: gray; hydrogen: white. Solvent molecules and counterions are not shown.

been confirmed by NMR spectroscopy. The ^1H and ^{13}C NMR signals of pseudorotaxane-terminated dendrimers **4** are broader than those of **3**. The line broadening becomes more pronounced in the higher generation dendrimers, which is attributable to a diminished molecular motion of the dendritic shells. ^1H NMR spin-lattice (T_1) relaxation measurements on **3** and **4** have been performed and the results are compared in Figure 3. The T_1 value for the methylene protons at the termini in **3** decreases slightly but steadily with increasing generations (Figure 3a). On the other hand, the T_1 value for the corresponding protons in **4** increases sharply with increasing generations (Figure 3b). Such an increase in the T_1 relaxation value with increasing generations indicates that the molecular motion in the outside dendritic shell of **4** resembles that in a solid phase.^[15] This unusual behavior has been observed only once in a dendrimer with a highly congested exterior.^[2i]

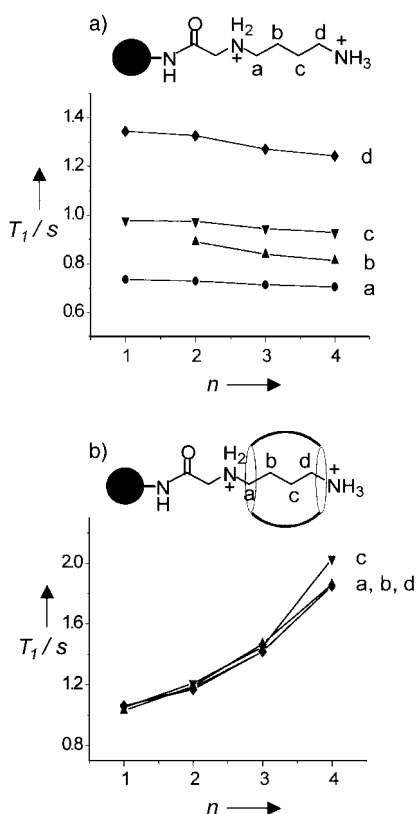


Figure 3. Generation (n) dependence of the ^1H NMR spin-lattice relaxation time (T_1) for the terminal diaminobutane unit of **3** (a) and **4** (b) in D_2O at 295 K. The proton relaxation data were recorded on a Bruker DRX500 at 500.23 MHz with a standard inversion–recovery pulse sequence.

In summary, we have synthesized novel pseudorotaxane-terminated dendrimers having a number of molecular beads threaded onto the periphery through noncovalent interactions. These pseudorotaxane-terminated dendrimers not only constitute a new class of topologically intriguing molecules but also provide a novel way of modifying the dendrimer exterior by noncovalent interactions. In addition, the large terminal pseudorotaxane units can form a rigid shell at the outer surface of the dendrimer which can potentially inhibit the escape of guest(s) trapped in the interior. If the beads can be de-threaded to make the exterior flexible once again and allow the escape of entrapped guests from the interior, such systems can potentially function as vehicles for translocating guests such as drug molecules. A preliminary experiment shows that all or a part of CB[6] molecular beads of **4** are de-threaded upon treatment with a base. We are currently investigating the threading/de-threading mechanisms as well as other properties of these novel dendrimers.

Experimental Section

Typical procedures for **2**, **3**, and **4** are illustrated with the third-generation dendrimers **2c**, **3c**, and **4c**.

2c: Dendrimer **1c** (124 mg, 0.074 mmol) and triethylamine (0.17 mL, 1.24 mmol) were added to activated ester **5** (0.7 g, 1.2 mmol) in dichloromethane (20 mL). The resulting solution was stirred for 24 h at room temperature. After addition of dichloromethane (50 mL) the solution was washed with water and NaHCO_3 solution, dried, and concentrated.

Purification by column chromatography using EtOAc and then CH_2Cl_2 :MeOH (1:1) containing 3% Et_3N as an eluent yielded the desired product **2c** (493 mg, 83%).

3c: A solution of **2c** (420 mg, 0.05 mmol) in 30% HBr–AcOH (10 mL) was stirred for 10 h at room temperature. Addition of diethyl ether (50 mL) to the solution precipitated **3c** (370 mg, 95%).

4c: CB[6] (128 mg, 0.13 mmol) was added in small portions to a solution of the dendrimer **3c** (50 mg, 6.7 μmol) in H_2O (30 mL) and the mixture was stirred for 10 h at room temperature. After excess cucurbituril was filtered, the volume of the solution was reduced to about 2 mL by evaporation. Addition of EtOH (30 mL) to the solution precipitated **4c** (152 mg, 97%).

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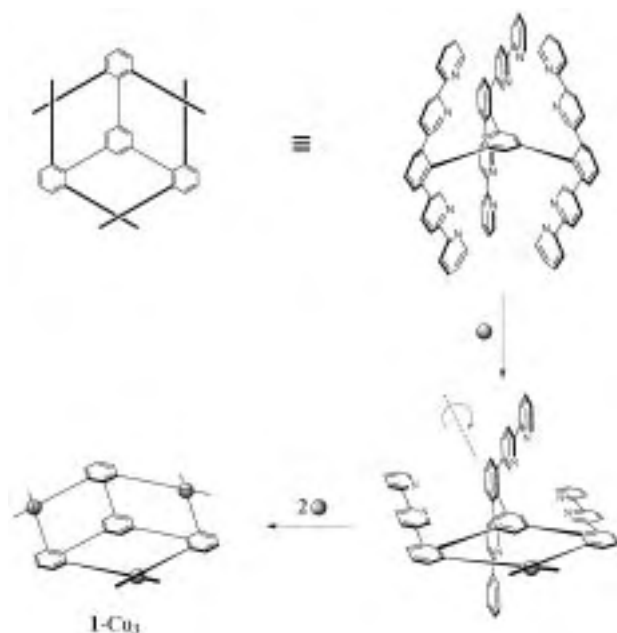
Trinuclear Copper(I)-bipyridine Triskelion: Template/Basculer Control of Coordination Complex Stereochemistry in a Trefoil Knot Precursor**

Craig R. Woods, Maurizio Benaglia, Shinji Toyota, Kenneth Hardcastle, and Jay S. Siegel*

Projection of a knotted structure in the plane can be oriented to reveal a principal core “crossing structure” and a periphery of connecting arcs. From that perspective, the retrosynthesis of molecular knots and links can be divided into problems related to the control of a) macrocyclizations and b) stereochemistry of “crossing structures”. Molecular designs that capitalize on symmetry and cooperativity lead to

efficient control of stereochemistry.^[1,2] In the double helicates, the regular helical structure provides cooperative reinforcement for each new metallostereocenter to be of uniform configuration.^[3] The identification of the double helix motif in a representation of the trefoil knot is key to understanding the rational synthesis where stereochemical control of helicity dictates the product identity, chirality, and yield.^[4–9] An alternative representation of the trefoil knot has a D_3 -symmetric core embedded within.^[10] This core is also common to the Borromean link motif.^[11–14] As such, synthesis and stereochemical control of an appropriate D_3 triskelion would provide a new class of stereoregular polynuclear coordination complexes and set the path to high-symmetry molecular knots and links.

Templating is a tried-and-true method for regulating the juxtaposition of molecular substructures.^[15–20] A bascule mechanism pivots about the midpoint of a beam and couples the motion of the two ends such that as one end raises the other lowers.^[21] Combining a tripodal template with tangential bascule beams readily evokes a D_3 -symmetric construct in which neighboring beam-ends can cross. If these beam-ends were bidentate ligands, their crossing points would constitute binding sites for metals with tetrahedral ligand fields. Thus, emerges a design for a trinuclear copper(I)–bipyridine triskelion (**1**) (Scheme 1). The triskelion comes from three equivalents of a crescent-shaped polyaryl (**2**) and a 1,3,5-triethynyl core.



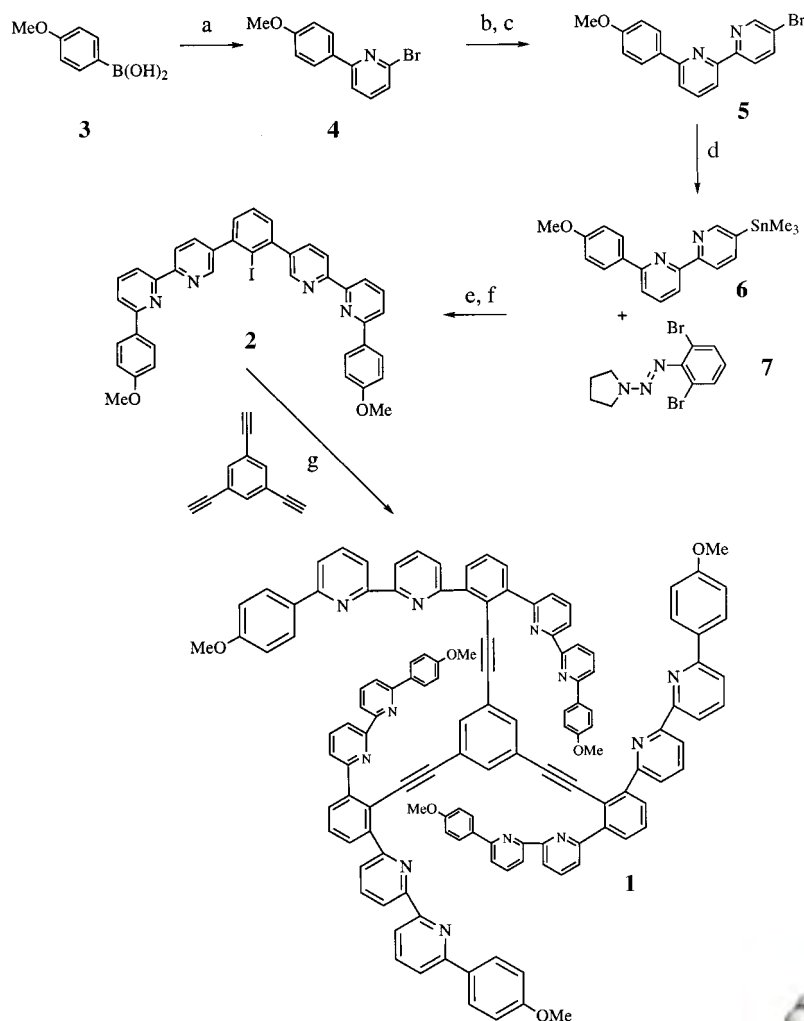
Scheme 1. Bascule mechanism for binding three metals in a triskelion. ● = Cu^I.

Synthesis of **1** depends heavily on the application of palladium-based Suzuki,^[22–24] Stille,^[25] and Sonogashira^[26] type aryl couplings (Scheme 2).^[27–29] Although one begins from anisyl boronic acid (**3**) and 2,6-dibromopyridine to form 6-anisyl-2-bromopyridine (**4**), the coupling strategy rapidly builds much larger products. The stannylation of **4** occurs by reaction with butyllithium at -78°C followed by quenching with trimethylchlorostannane. This stannyl reagent reacts

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Scheme 2. Synthesis of **1**: a) 2,6-dibromopyridine, $[\text{Pd}(\text{PPh}_3)_4]$, Na_2CO_3 , toluene, reflux, 74 %; b) 1) BuLi , Et_2O , -78°C , 2) Me_3SnCl , 85 %; c) 2,5-dibromopyridine, $[\text{Pd}_2(\text{dba})_3]$, AsPh_3 , DME, reflux, 57 %; d) $\text{Me}_3\text{SnSnMe}_3$, $[\text{Pd}(\text{PPh}_3)_4]$, DME, reflux, 57 %; e) $[\text{Pd}(\text{PPh}_3)_4]$, DME, reflux, 66 %; f) I_2 , dichloroethane, reflux, 78 %; g) $[\text{PdCl}_2(\text{PPh}_3)_2]$, Et_3N , THF, reflux, 51 %. dba = dibenzylideneacetone.

regioselectively with the 2 position of 2,5-dibromopyridine to give 6'-anisyl-5-bromobipyridine (**5**). Problems with the stannylation of **5** led to the development of a direct stannylation procedure, which employs hexamethyldistannane and catalytic amounts of palladium in dimethoxyethane (DME).^[30] The 5-stannyl derivative **6** coupled cleanly with the dibromophenyltriazene **7**, and, after conversion of the triazine functionality to the iodide with iodine in refluxing dichloroethane,^[31] **2** was obtained. Sonogashira coupling of three equivalents of **2** with 1,3,5-triethynylbenzene yielded the desired D_3 -symmetric ligand,^[26] which readily bound copper(I) in acetonitrile solution (**1-Cu₃**).

The characteristic deep red color of **1-Cu₃** was the first sign of successful complexation, and electrospray mass spectrometry confirmed molecular mass and composition, but neither could prove our goal: control of stereochemistry. Additional evidence came from the ^1H and ^{13}C NMR spectra that display the limited set of signals one would associate with D_3 symmetry. The X-ray crystal structure of **1-Cu₃** complemented

the solution work and showed the successful template/basculc construction (Figure 1).^[32] Thus, barring anomalous crystal forces in combination with dynamic averaging in the solution NMR spectra, the idealized structure of **1-Cu₃** is D_3 -symmetric in all chemical phases, as designed.^[33, 34]

Inspection of the structural details reveals that the bipyridine arms from neighboring units cross to form the envisioned tetrahedral metal binding sites. The overall structure is distorted away from D_3 symmetry; but this distortion is most likely the result of crystal packing forces. The bond lengths and bond angles are in good agreement with standard values.

The bascule mechanism ensures that the stereochemical configuration set during the binding of the first metal ion dictates the same configuration for the remaining sites. A related question is whether that initial metal binding also promotes subsequent metal bindings (positive cooperativity).^[35] Titration of **1** with Cu^{I} ions leads to clean isosbestic behavior consistent with an intermediate-free transformation. Indeed, when observing the process by NMR spectroscopy, addition of a given fraction of the complement of three Cu^{I} ions leads to that fraction of **1-Cu₃** and free **1** with no other species or intermediates (Figure 2). These two sets of data provide strong

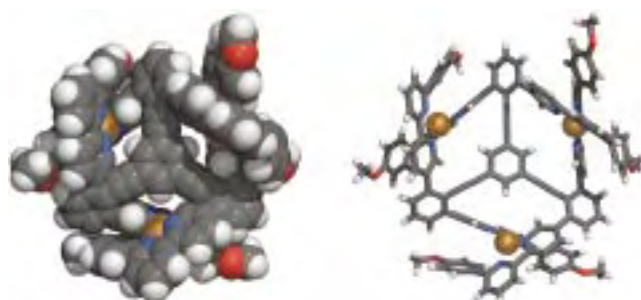


Figure 1. Space-filling (left) and framework (right) representation down the C_3 axis of the crystal structure of **1-Cu₃**.

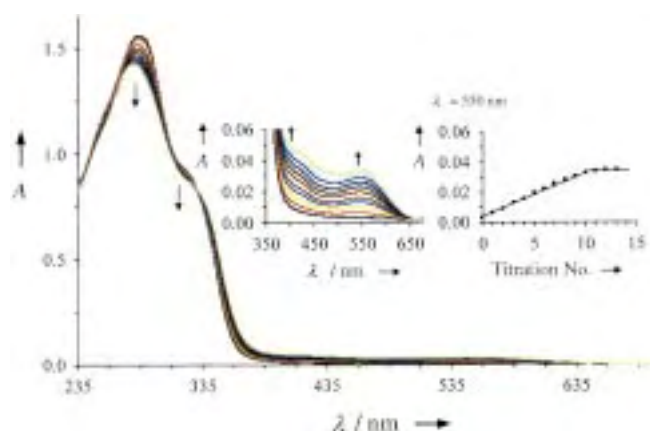


Figure 2. UV/Vis titration of **1** with copper(I) tetrafluoroborate. Left inset: enlargement of 350–650 nm; right inset: Scatchard plot of absorbance vs. metal equivalents at 550 nm.

evidence for positive cooperativity among the metal binding sites in **1**-Cu₃.

Thus, metal-binding properties of **1** and the high symmetry of **1**-Cu₃ illustrate a high degree of control over the degree and regularity of molecular entwinement. In combination with an appropriate macrocyclization method, the stage is set for the directed synthesis of complex topological stereoisomers of high symmetry, specifically, a molecular trefoil knot.^[36]

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remaining non-H atoms by LS – ΔF syntheses, refinement against F^2 (SHELXL) with all H atoms included in idealized positions, all Cu, O, and F atoms refined anisotropically. Structure solution, refinements, graphics, and tables calculations performed with SHELXTL/PC. **1**: C₁₃₂H₉₀B₃Cu₃F₁₂N₁₂O₆, M_r 2391.21, monoclinic, space group $P2_1/c$ (no. 14), $a = 24.879(2)$, $b = 14.4764(12)$, $c = 37.097(3)$ Å, $\beta = 102.912(1)^\circ$, $V = 13023(2)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.220$ g cm^{–3}, $\mu(\text{MoK}\alpha) = 0.558$ mm^{–1}, crystal dimensions ca. $0.15 \times 0.06 \times 0.06$ mm³, $2\theta_{\text{max}} = 38.6^\circ$, 37667 reflections measured, 9851 unique reflections ($R_{\text{int}} = 0.149$), 770 parameters, 3 restraints, $R_1(wR_2) = 0.1163$ (0.2624) for 5498 reflections with $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-148313. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Tetranuclear Copper(II)-Biphenanthroline Gridwork: Violation of the Principle of Maximal Donor Coordination Caused by Intercalation and CH-to-N Forces**

Shinji Toyota, Craig R. Woods, Maurizio Benaglia, Richard Haldimann, Kenneth Wärnmark, Kenneth Hardcastle, and Jay S. Siegel*

The amelioration of “hot spots” in a molecule through specific molecular association is a general chemical principle, which has been recently highlighted as a driving force for “supramolecular” reactions.^[1] The instability of unpaired radicals, uncoordinated metal ions and ligands, and unasso-

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evidence for positive cooperativity among the metal binding sites in **1**-Cu₃.

Thus, metal-binding properties of **1** and the high symmetry of **1**-Cu₃ illustrate a high degree of control over the degree and regularity of molecular entwinement. In combination with an appropriate macrocyclization method, the stage is set for the directed synthesis of complex topological stereoisomers of high symmetry, specifically, a molecular trefoil knot.^[36]

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remaining non-H atoms by LS – ΔF syntheses, refinement against F^2 (SHELXL) with all H atoms included in idealized positions, all Cu, O, and F atoms refined anisotropically. Structure solution, refinements, graphics, and tables calculations performed with SHELXTL/PC. **1**: C₁₃₂H₉₀B₃Cu₃F₁₂N₁₂O₆, M_r 2391.21, monoclinic, space group $P2_1/c$ (no. 14), $a = 24.879(2)$, $b = 14.4764(12)$, $c = 37.097(3)$ Å, $\beta = 102.912(1)^\circ$, $V = 13023(2)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.220$ g cm^{–3}, $\mu(\text{MoK}\alpha) = 0.558$ mm^{–1}, crystal dimensions ca. $0.15 \times 0.06 \times 0.06$ mm³, $2\theta_{\text{max}} = 38.6^\circ$, 37667 reflections measured, 9851 unique reflections ($R_{\text{int}} = 0.149$), 770 parameters, 3 restraints, $R_1(wR_2) = 0.1163$ (0.2624) for 5498 reflections with $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-148313. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Tetranuclear Copper(II)-Biphenanthroline Gridwork: Violation of the Principle of Maximal Donor Coordination Caused by Intercalation and CH-to-N Forces**

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The amelioration of “hot spots” in a molecule through specific molecular association is a general chemical principle, which has been recently highlighted as a driving force for “supramolecular” reactions.^[1] The instability of unpaired radicals, uncoordinated metal ions and ligands, and unasso-

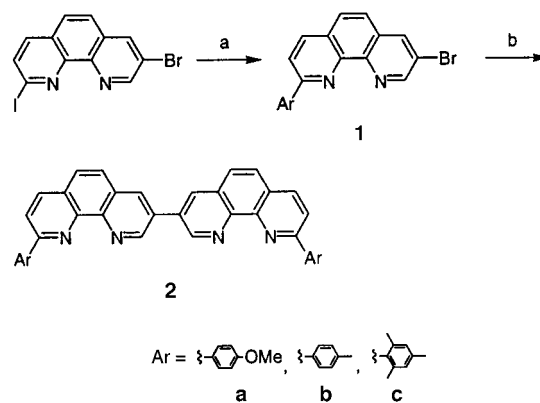
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ciated hydrogen bond acceptors and donors attest to the generality of such chemical assembly phenomena. From such empirical wisdom, “rules” were developed for supramolecular design, such as the principle of maximum coordination, in which it is assumed that a metal ion with a defined ligand field will associate with enough donor atoms to satisfy that field, and that no donor atoms will be left uncoordinated.^[2, 3] Though trivial for monodentate ligands, this principle has provided a rationalization for the structures found in several metal-coordination arrays.^[4–10] A signal example in this area has been the molecular grids,^[11] wherein n rods of m bidentate ligands coordinate $(n \times m)/2$ tetrahedral metal ions.^[3, 11–13] The stoichiometry in such complexes is uniformly $L_nM_{(n \times m)/2}$, for example, a 2×2 grid from a bisbipyridine rod (Scheme 1).^[14] The regularity of this composition has evoked the idea of algorithmic or programmed molecular association.^[15, 16] Despite the appeal of such imagery, the diversity of association forces in chemistry complicates the molecular algorithm to an extent where the analogy between modern computer scripts and supramolecular design is unwarranted. To this point, we present a simple metal–ligand combination that highlights the limitations of such “programs”.

Among bidentate ligands, 1,10-phenanthroline is renowned for the generality of its stable metal complexes.^[17, 18] In particular, copper(I) and silver(I) form stable tetrahedral complexes with 1,10-phenanthroline.^[19, 20] Rods of 3,8-linked oligophenanthrolines should therefore provide excellent scaffolds for the creation of molecular grids. Recent methods in phenanthroline halogenation provided a route to a series of 2-aryl-8-bromo-1,10-phenanthrolines **1a–c**,^[21] which, through reductive homocoupling mediated by nickel(0),^[22] formed the 2,2'-diaryl-8,8'-bis-1,10-phenanthrolines (Scheme 2) (**2a–c**).

Combination of a suspension of **2a** in acetonitrile with copper(I) or silver(I) produces a red (**3a**-Cu) or colorless (**3a**-Ag) homogeneous solution, respectively. In each case, all the signals in the ^1H and ^{13}C NMR spectra are sharp and can be assigned to two sets of phenanthroline resonances in a ratio of 2:1. Such spectra imply that there are two different kinds of environments for the biphenanthroline rods in the complex but that each rod is symmetric about its midpoint. Variations in counterion, molecular equivalents, or solvents have little effect on the spectra. No single M_nL_n molecular grid, weave, or cycle has the symmetry necessary to account for the complexity and relative amounts of the specific signals seen in these spectra, even with consideration of dynamic processes. Persistence of the general spectral qualities and precise 2:1 ratio seriously restricts the likelihood of multiple species in

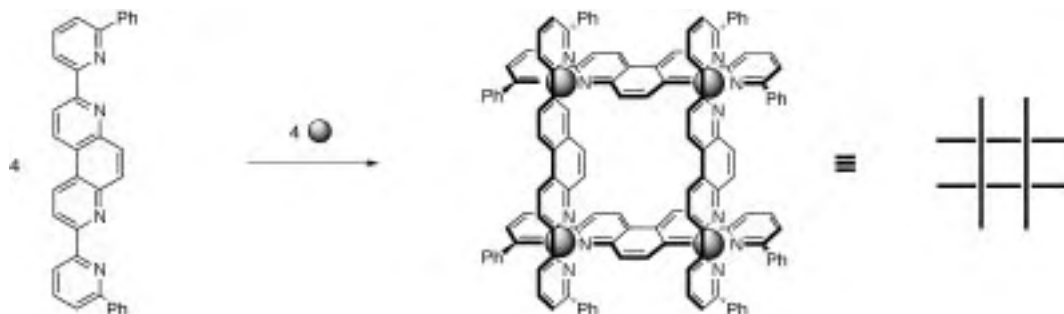


Scheme 2. a) Arylboronic acid, $[\text{Pd}(\text{PPh}_3)_4]$, $\text{Ba}(\text{OH})_2$, 1,2-dimethoxyethane, H_2O , reflux; b) $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, PPh_3 , Zn, DMF, 50°C .

equilibrium. Electrospray mass spectrometry provides a crucial clue to solve the mystery of the structure in solution; the molecular ion corresponds to the formula $M^+_4L_6A^-_4$, in violation of the $L_nM_{(n \times m)/2}$ rule!

Even the clarification of molecular stoichiometry does not provide an immediate solution to this “structural algorithm.” The principle of maximum coordination might seduce one to search for hexacoordinate solutions if not for the sacrilegious sound of octahedral copper(I)! Ultimately, crystal structure analysis brought this chemical regression to self-consistency: **3a**-Cu is a 3×3 molecular grid possessing 4 ligands coordinatively bonded to metal ions in the form of a molecular square (host) with 2 additional ligands filling the interstitial spaces (guest) (Figure 1).^[23] Given this unanticipated “output,” a closer inspection of the molecular program seems warranted.

From the crystal structure of $(\mathbf{3a}\text{-Cu})^{4+} \cdot 4\text{BF}_4^-$, we see two striking elements of molecular complementarity: 1) the grid spacing between host biphenanthroline rods is about $7.5 \text{ \AA}$ on average and therefore well accommodates an additional rod as an aromatic guest by intercalation; 2) the “uncoordinated” nitrogen atoms of the guest biphenanthrolines are positioned within van der Waals contacts of one set of C9,C9' hydrogen atoms of the host scaffold. Effects that account for the stability of the complex must include primarily dispersive and to a lesser extent electrostatic interactions among the π clouds (“ π stacking”).^[24–31] Coincidentally, a complimentary electrostatic interaction between the hydrogen atoms of C9 on the scaffold and the nitrogen atoms of the guest exists. Some would herald the proximity of aromatic hydrogen atoms and phenanthroline nitrogen atoms as



Scheme 1. Simple 2×2 grid a la Baxter et al. $\bullet = \text{Cu}^I$.

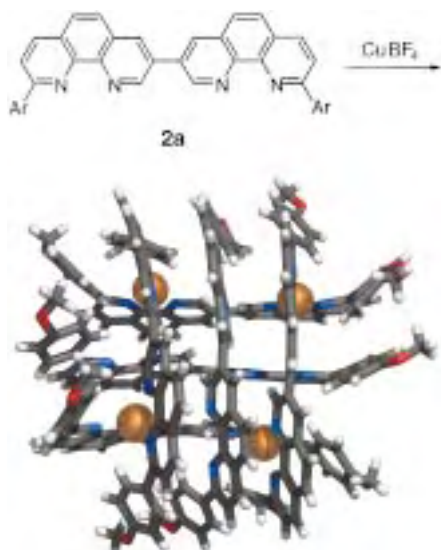


Figure 1. X-ray structure of the host–guest 3×3 grid **3a**-Cu.

evidence for CH–N hydrogen bonds;^[32, 33] however, it should be kept in mind that the molecular complex is an equilibrium structure that balances all molecular forces. Thus, if attraction among the π systems was great enough, the energy benefit of intercalation could force the proximity of nitrogen and hydrogen even at the energy cost of local repulsive interactions.^[34]

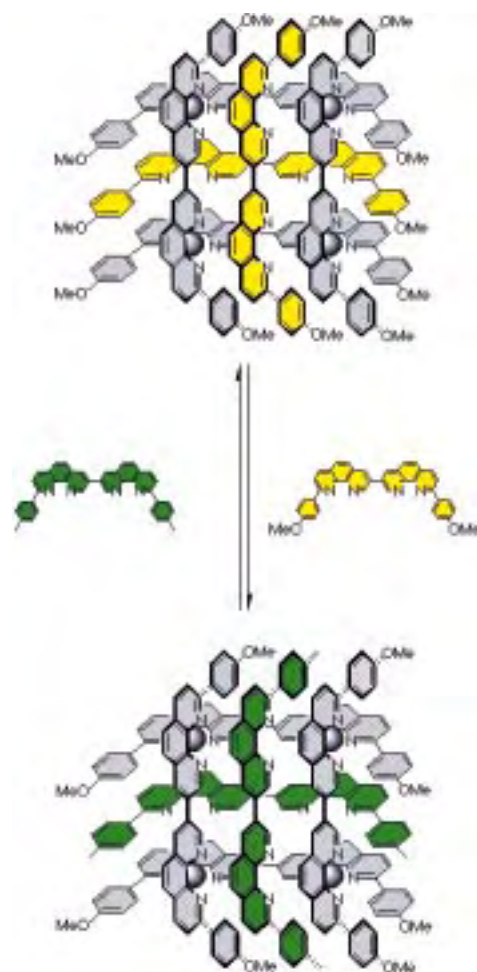
Variation in the aryl substituent affords us some control over this grid motif. Whereas the simple electronic perturbation of swapping anisyl for tolyl leads to a similar 3×3 grid complex, **3b**-Cu, the steric/conformational perturbation of the mesityl group does not produce a grid architecture. The mesityl groups twist out of the plane of the biphenanthroline ligand and jut their *ortho* methyl groups into the interstitial spaces, precluding intercalation by another ligand and leading to an instability of the grid architecture. Thus, it is not simply that a “stable” 2×2 grid is formed and the guests then fit in,^[14] but rather there must be a cooperativity between the host and guest components that gives **3**-Cu its unique supramolecular structure.

Several additional questions are raised by this simple system: What is the nature of complex stability? Is the free ligand the best guest for the host grid? What is the mechanism/time scale for grid formation? Access to two related complexes, **3a**-Cu and **3b**-Cu, provided some avenues to investigate. High-temperature NMR spectra (150 °C) of the pure complexes show no coalescence of the signals and set a lower limit on exchange barrier of host and guest ligands to about 20 kcal mol⁻¹. In contrast, a mixture of **3a**-Cu and **3b**-Cu could not be prepared fast enough to preclude scrambling of the guest ligands. Thus, the barrier to exchange could not be higher than 25 kcal mol⁻¹.

The previous two studies focused on complex to complex exchange, but one can also probe the exchange between free ligand and the guest site of the complex (Scheme 3). Addition of free **2b** to a solution of **3a**-Cu results in rapid exchange of guest followed by a slower incorporation into the host sites. By supporting the complex on alumina and passing a solution of free ligand over the stationary complex, a pure “mixed”

host–guest complex could be formed—with either **2b** intercalated in place of **2a** in **3a**-Cu or **2a** intercalated in place of **2b** in **3b**-Cu—and then isolated by stripping the complex quickly from the alumina.

The dynamics of the guest-exchange process were studied in more detail by spin saturation transfer spectroscopy. In the spectrum of a solution of ligand **2a** and complex **3a**-Cu, the methyl protons of **2a** are irradiated and the transfer of magnetization is found only in the guest site of **3a**-Cu. Quantitative measure of the amount of magnetization transferred and the relaxation time of the protons led to a rate of exchange.^[35] Assuming a disassociative mechanism with the first step rate limiting, the rate measured is for the unimolecular disassociation of the guest ligand from **3a**-Cu. From the rate data measured over a 20 degree range, a free energy of activation around 21 kcal mol⁻¹ could be deduced and a crude partitioning indicates that at room temperature about 75% of the energy barrier is enthalpic (ca. 15 kcal mol⁻¹). Notably, the entropy for the disassociation is positive and large (ca. 20 cal K⁻¹ mol⁻¹). This unusual entropy hints at a novel solvation effect akin to the hydrophobic effect in water; the disassociated guest and host exposes a significantly larger combined surface area for solvation and cavitation than the host–guest supramolecule.



Scheme 3. Exchange reaction of guest ligands.

In conclusion, the concept of an accessible and controllable molecular program, even within the limited arena of metal coordination structures, seems premature. If one wants to “program” in the “machine language” of molecules, (s)he will receive the greatest insight from the firm fundamentals of thermodynamics and kinetics as opposed to distractions of sirenous supramolecular slogans.

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Synthesis and Fluorescence Properties of Manisyl-Substituted Terpyridine, Bipyridine, and Phenanthroline**

Jon C. Loren and Jay S. Siegel*

Cation affinity, solubility, and spectroscopy (e.g. fluorescence) are three characteristic physical properties of oligopyridine-based heterocycles (2,2':6',2''-terpyridines, 2,2'-bipyridines, and 1,10-phenanthrolines, in the following simply designated as terpyridines, bipyridines, and 1,10-phenanthrolines) that one would like to control through a simple synthesis scheme from common building blocks.^[1] In particular, aryl-substituted heterocycles of this family have a rich history in metal coordination chemistry.^[2–3] Their conjugated backbones make them attractive chromophores and molecular “antennae”;^[4–7] however, the larger and fused analogues typically suffer from poor solubility and inefficient chemical syntheses. Among aryl substituents, *p*-anisyl (4-methoxyphenyl) has been extensively used where further structural elaboration was desired,^[8–10] and manisyl has been noted for endowing superior solubility features.

A hybrid of these two aryl motifs, 4-methoxy-2,6-dimethylphenyl or “manisyl”, offers both characteristics, but has been

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

virtually absent as a substituent in this family of heterocyclic compounds. Here we present a general route to these aryl-substituted heterocycles using palladium-mediated coupling of organozinc halides with heterocyclic halides, and note an extraordinary suitability of zinc to complex with the in situ forming ligand, thus protecting the catalyst from poisoning and simplifying product purification. A further highlight of this work stems from the ability of the manisyl group to endow specific members of this family with high fluorescence quantum efficiency. Therefore, in one concentrated effort we have been able to address problems related to the chemical synthesis, physical manipulation, and photophysical properties of these versatile metal chelates.

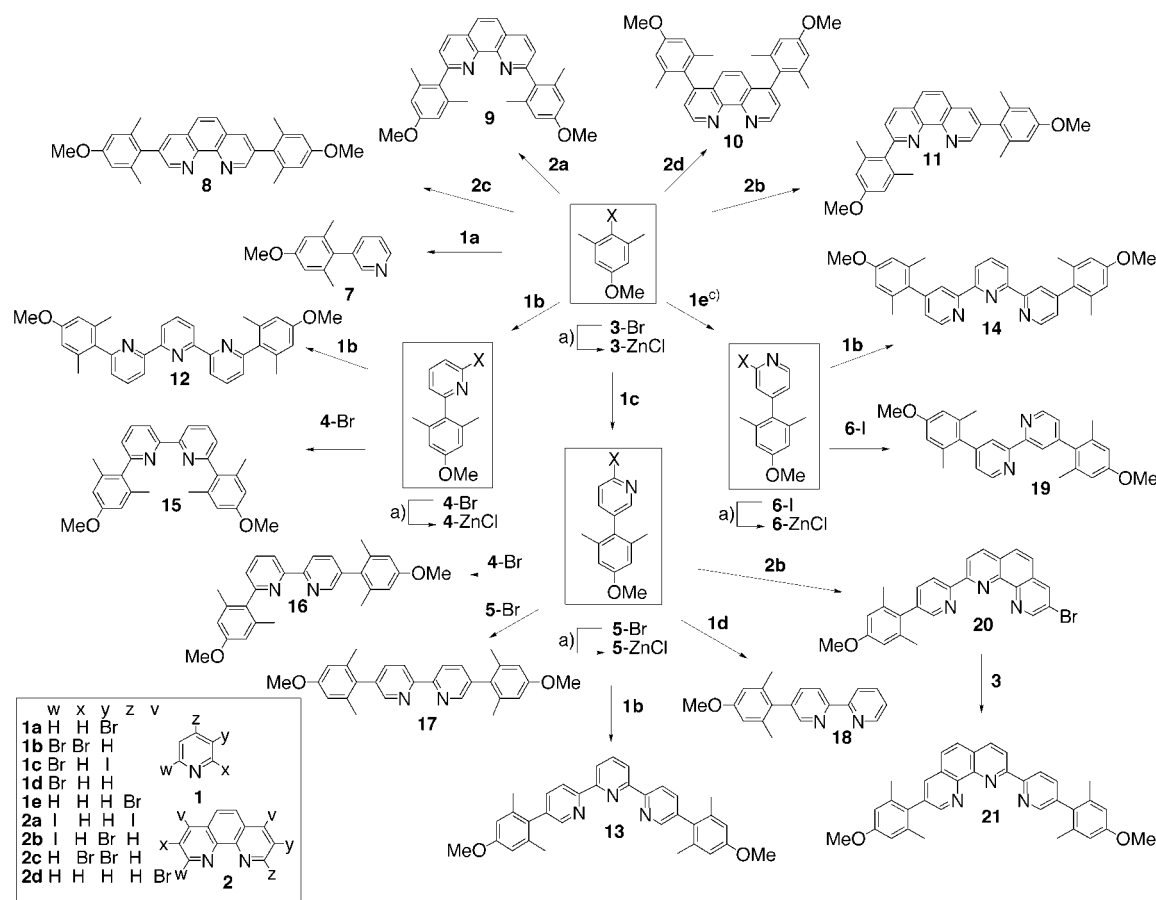
Considering substitution at the α , β , and γ positions relative to the nitrogen atom of a pyridine and including the combinations of pyridine and phenanthroline up to tridentate chelates (pyridine, bipyridine, terpyridine, phenanthroline, and pyridylphenanthroline) generates a family of 42 structures, from which a representative subset of 17 were targeted for synthesis, with manisyl as the prototypical substituted arene. An appropriate set of halogenated pyridines (**1a–e**) and phenanthrolines (**2a–d**) were available either commercially or from literature procedures.^[11–15] Starting from commercially available 3,5-dimethylanisole, the literature-known 4-methoxy-2,6-dimethylbromobenzene (**3-Br**) was prepared^[16] and then converted into the organozinc reagent **3-ZnCl** by employing Negishi conditions.^[17–19] Halopyridines **1a–c** and **1e** react smoothly with one molar equivalent of **3-**

ZnCl to form the corresponding arylpyridines, of which **4-Br**, **5-Br**, and **6-I** can be converted to the organozinc analogue.^[20] These six sets of building blocks can be permuted between organozinc and halide counterparts in a series of Negishi couplings to generate a large array of ligand patterns (Scheme 1). For example, symmetrical terpyridines (**12–14**) were prepared from two molar equivalents of an organozinc and **1b** in about 60 % yield (Table 1).

Table 1. Substrates and yields for the synthesis of heterocycles **7–21**.

Aryl–ZnCl	Aryl–X	Product	Yield [%] ^[a]	Melting range [°C] ^[b]
3-ZnCl	1b	4-Br	61	75–77
3-ZnCl	1c	5-Br	85	78–80
3-ZnCl	1e	6-H	98	98–100
3-ZnCl	1a	7	75	53–54
3-ZnCl	2c	8	70	248–249
3-ZnCl	2a	9	69	234–235
3-ZnCl	2d	10	15	255 (decomp)
3-ZnCl	2b	11	67	244–245
4-ZnCl	1b	12	50	215–216
5-ZnCl	1b	13	62	224–225
6-ZnCl	1b	14	11	272–274
4-ZnCl	4-Br	15	59	231–233
5-ZnCl	4-Br	16	31	164–166
5-ZnCl	5-Br	17	59	257–258
5-ZnCl	1d	18	59	94–96
6-ZnCl	6-I	19	21	272–274
5-ZnCl	2b	20	77	112–118
3-ZnCl	2b	21	81	130–134

[a] Yields based on isolated product after purification. [b] Melting points are uncorrected.



Scheme 1. a) *n*-Butyllithium, -78°C , THF; ZnCl₂, THF, $-78^{\circ}\text{C} \rightarrow \text{RT}$; b) Aryl–X, 5 % [Pd(PPh₃)₄], reflux, 12 h, THF; c) see ref. [20].

A special highlight of the method was the ease with which the peculiar pyridylphenanthroline **21** was prepared as a highly soluble terpyridine analogue.^[21] In some cases the zinc complex of the ligand precipitates at the end of the reaction. This solid can be readily separated from the organic by-products after which the zinc cation can be removed by an EDTA extraction to leave the pure ligand. In addition, all compounds prepared could be isolated in pure form by column chromatography on alumina with hexanes/dichloromethane. The transferability of reaction conditions across this series of derivatives indicates that this method is generally applicable to the synthesis of any aryl/alkyl cognate that will tolerate the formation/presence of organozinc halides.^[22, 23]

The solubility of all manisyl derivatives in organic solvents is superior to that of the simple phenyl- or anisyl-substituted heterocycles (e.g., the solubility of dimanisyl terpyridine **13** compared to that of its anisyl cognate in chloroform, dichloromethane, tetrahydrofuran and acetone are 230, 210, 95, and 10 mg mL⁻¹ versus 2, >1, >1, >1 mg mL⁻¹, respectively). Facile deprotection of the methoxy group by pyridinium hydrochloride has been demonstrated for terpyridine **13**, and the resulting phenolic derivative remains soluble. Realkylation of the phenolic oxygens occurred by standard methods (e.g. allyl bromide in the presence of potassium carbonate in acetonitrile) without problems, which makes it clear that these ligands will be directly applicable to the synthesis of larger supramolecular coordination complexes and will be instrumental in the elaboration of new topological stereoisomers^[9, 24] and materials incorporating metal binding sites.^[25]

Presumably the solubility of the manisyl derivatives stems from the orthogonal conformation at the aryl–pyridyl bond due to the proximal methyl groups. This conformation should also prohibit the effectiveness of normal planar conjugation. Curiously, terpyridine **13** displays a very bright fluorescence (λ_{em} 408 nm; λ_{max} 286 nm) with a quantum yield (Φ_f) of 0.85 in acetonitrile and retains fluorescence in water.^[26, 27] The possibility of a type of spiroconjugation or twisted excited state electron transfer thus arises.^[27, 28] The ease of the synthetic method provided access to a large swath of structural space and the ability to probe structural dependence of this fluorescence behavior. Classifying the quantum yields for the 17 representative ligands as high ($\Phi_f > 0.75$), medium ($0.25 < \Phi_f < 0.75$), and low ($\Phi_f < 0.25$), one immediately sees that manisyl substitution β to the nitrogen atom is a common structural feature of the high quantum yield group, **13**, **17**, and **18** (Figure 1).^[29] The control comparison of pyridine **7** with bipyridine **18** shows low and high efficiency, respectively, and establishes the principal “minimum” chromophore. The compounds of medium quantum yield (**8**, **16**, and **21**) also bear a manisyl group in the β position. Substitution only α or only γ resulted in quantum yields significantly lower than 20%, with the γ set slightly more efficient than the α set. Protonation of the heterocycle results in a standard red shift of about 30–100 nm in the absorption spectrum and emission maxima. The presence of zinc as a complexing metal causes a shift in the spectra of the ligands in the high- and medium-efficiency group (Table 2). Protonation and metalation display clean isosbestic behavior. A full

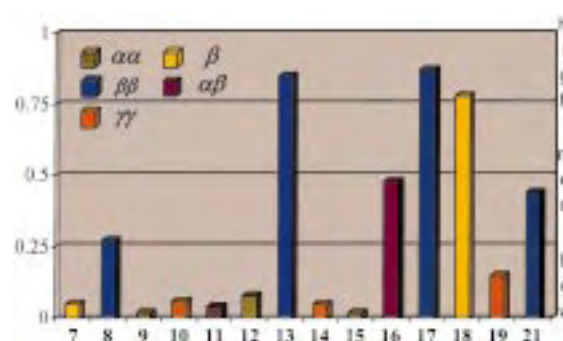


Figure 1. Bar graph of fluorescence quantum yield for heterocycles **7**–**21**.

Table 2. Excitation and emission wavelengths of free ligands (L), selected protonated ligands (L-H⁺),^[a] zinc-bound ligands (L-Zn²⁺),^[b] and fluorescence quantum yields (Φ_f)^[c] recorded in CH₃CN.

	L	L	Φ_f	L-H ⁺	L-H ⁺	L-Zn ²⁺	L-Zn ²⁺
	λ_{ex} [nm]	λ_{em} [nm]		λ_{ex} [nm]	λ_{em} [nm]	λ_{ex} [nm]	λ_{em} [nm]
7	285	358	0.05				
8	270	405	0.27	356	449	322	486
9	266	380	0.02				
10	267	412	0.06				
11	270	383	0.04				
12	284	412	0.08				
13	286	408	0.85	368	535	340	512
14	279	417	0.05				
15	282	408	0.02				
16	290	409	0.48	350	532	314	516
17	296	408	0.87	350	569	320	491
18	286	410	0.78	310	499	308	496
19	282	414	0.15				
21	296	443	0.44	368	541	366	537

[a] Excess CH₃SO₃H. [b] Excess ZnCl₂. [c] Measured relative to 9,10-diphenylanthracene.

analysis of the fluorescence behavior as a function of aryl substitution is underway.

In conclusion, a simple general procedure for the synthesis of α -, β -, and γ -substituted bipyridines, terpyridines, phenanthrolines, and pyridylphenanthrolines has been developed on the basis of palladium-mediated coupling of organozinc halides and halogenated heterocycles. The method has been showcased with the “manisyl” (4-methoxy-2,6-dimethylphenyl) group as the aryl prototype. The manisyl group adds desirable functionality that results in facile chemical elaboration, superior solubility and high fluorescence quantum yield. The compounds prepared here are representative of a much larger class of imaginable aryl-substituted heterocycles that will be important ligands for metal chelation, supramolecular complexation, topological isomer construction and fluorophore generation.^[30, 31] Such auspicious spectral and complexation features point to the use of such compounds in recognition,^[32] sensor,^[32] tagging,^[33] and catalytic applications.^[34]

Experimental Section

21:^[35] To a solution of **3-Br** (0.206 g, 0.957 mmol) in THF (20 mL) at –78 °C was added *n*BuLi (0.60 mL of a 1.6 M solution in hexane, 0.96 mmol). To this mixture was added a 0 °C solution of zinc chloride (0.130 g, 0.96 mmol) in THF (5 mL) by cannula and allowed to warm to room temperature.

Subsequently, a solution of **20** (0.300 g, 0.638 mmol) and [Pd(PPh₃)₄] (0.055 g, 0.048 mmol) in THF (5 mL) was added to the organozinc intermediate by cannula. The mixture was heated at reflux for 20 h, cooled to room temperature, and placed in a freezer. The white precipitate was filtered, washed with cold THF, and dried. The precipitate was dissolved in dichloromethane and extracted vigorously with saturated aqueous EDTA and basified with saturated aqueous sodium bicarbonate. The organic layer was separated, dried over magnesium sulfate, filtered, and evaporated to afford a white crystalline solid (270 mg, 81 %), m.p. 130–134 °C. ¹H NMR (300 MHz, CDCl₃): δ = 9.05 (d, *J* = 2.0 Hz, 1H), 9.04 (d, *J* = 8.0 Hz, 1H), 8.83 (d, *J* = 8.5 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H), 8.41 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.72 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.74 (s, 2H), 6.70 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 2.07 (s, 6H), 2.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 158.85, 158.67, 156.12, 154.37, 151.80, 149.63, 145.51, 144.67, 138.38, 137.83, 137.67, 136.89, 136.41, 135.84, 130.23, 130.01, 128.66, 128.49, 126.62, 122.41, 120.56, 112.88, 112.82, 55.23, 55.20, 21.43, 21.34; UV/Vis (CH₃CN): λ_{max} (ε) = 240 (6.3 × 10⁴), 296 (4.3 × 10⁴), 354 (8.7 × 10³) nm; HR-MS: *m/z*: calcd for C₃₅H₃₁N₃O₂: 525.2416; found: 525.2407.

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Parallel Reactions for Enantiomeric Quantification of Peptides by Mass Spectrometry**

W. Andy Tao and R. Graham Cooks*

The accelerating trend towards the use of enantiomerically pure compounds as drugs has underscored the need for new methods of enantioselective synthesis and chiral analysis.^[1] The capabilities of mass spectrometry for the rapid analysis of complex mixtures have encouraged its exploration for gas-phase chiral recognition.^[2] This has been achieved by direct measurement of the relative abundance of two diastereomeric ions formed by complexing enantiomers and a chiral reference,^[2d,g-i] ion–molecule reactions of diastereomeric adducts,^[2c,e] or collisional dissociation of diastereomers.^[2b] Quantitative analysis, especially when one enantiomer comprises only a few percent of a mixture, remains a challenge. Competitive reactions of two enantiomers toward a chiral reference are unavoidably influenced by the relative concentrations of the enantiomers, which affects the accuracy of the measurement of the enantiomeric excess (*ee*) unless the selectivity factor *s* (the ratio of competing rate constants) is

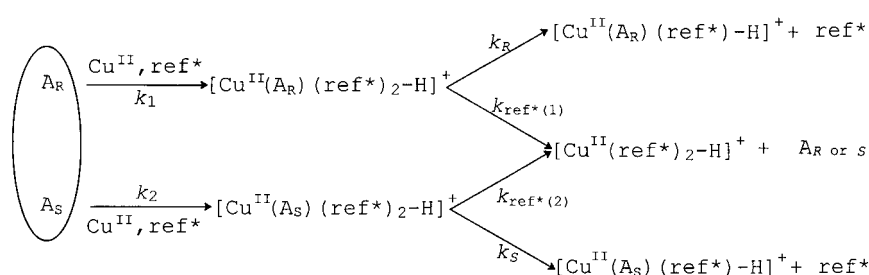
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extremely large. Taking condensed-phase kinetic resolution as an example, s must be at least 200 for resolution at 96% ee , and 500 at 98% ee .^[3] Such selectivities are currently beyond the reach of most condensed-phase reactions,^[4] let alone gas-phase reactions, which usually display lower selectivities.^[5]

We describe here a novel gas-phase method for rapid chiral quantification at low ee values by using a simple technique in which chiral analysis is performed on the basis of two parallel ion–molecule reactions followed by low-energy dissociations. High selectivity is not required to quantify enantiomers at low ee values. A solution containing two enantiomers (A_R and A_S) is transformed into gas-phase cluster ions $[\text{Cu}^{\text{II}}(A_R)(\text{ref}^*)_2 - \text{H}]^+$ and $[\text{Cu}^{\text{II}}(A_S)(\text{ref}^*)_2 - \text{H}]^+$ through electrospray ionization (ESI; Scheme 1). The experiments



Scheme 1.

are done by simply mixing the analyte with a copper salt (CuCl_2) and a chiral reference compound (ref^*) in aqueous methanol. The relative abundances of $[\text{Cu}^{\text{II}}(A_R)(\text{ref}^*)_2 - \text{H}]^+$ and $[\text{Cu}^{\text{II}}(A_S)(\text{ref}^*)_2 - \text{H}]^+$ are found to reflect the enantiomeric composition of the analyte A in solution. Each cluster ion then undergoes competitive collision-induced dissociation (CID) in a quadrupole ion trap to form the dimeric complexes $[\text{Cu}^{\text{II}}(A)(\text{ref}^*) - \text{H}]^+$ and $[\text{Cu}^{\text{II}}(\text{ref}^*)_2 - \text{H}]^+$ by the loss of the neutral reference compound ref^* and analyte A , respectively. Depending on the configuration of analyte A , the stabilities of the diastereomeric ions $[\text{Cu}^{\text{II}}(A)(\text{ref}^*) - \text{H}]^+$ can be different, which results in different abundances in the mass spectra relative to the abundance of $[\text{Cu}^{\text{II}}(\text{ref}^*)_2 - \text{H}]^+$. The independent dissociation steps provide a measure of chiral composition but there is no mutual influence on either the formation or the dissociation of the trimeric cluster ions $[\text{Cu}^{\text{II}}(A_R)(\text{ref}^*)_2 - \text{H}]^+$ and $[\text{Cu}^{\text{II}}(A_S)(\text{ref}^*)_2 - \text{H}]^+$ generated from the individual optical isomers. Therefore, the overall chiral analysis is simply a function of the initial concentrations of the two enantiomers. Analogies can be drawn between this approach and the condensed-phase “parallel kinetic resolution” experiment introduced recently by Vedejs and Chen.^[6] The relative abundance ratio R [Eq. (1)] can be used to determine the enantiomeric composition of the analyte, provided a calibration curve is constructed.

$$R = \frac{[\text{Cu}^{\text{II}}(A)(\text{ref}^*) - \text{H}]^+}{[\text{Cu}^{\text{II}}(\text{ref}^*)_2 - \text{H}]^+} \quad (1)$$

We demonstrate the capability of this method with the quantification of several chiral peptides in this first report on chiral recognition and quantification of peptides using mass spectrometry. The copper(II) ion is selected as the central ion because of its ability to form polydentate complexes with

amino acids or peptides, thus promoting chiral recognition according to the “three-point interaction” rule.^[7] The degree of chiral discrimination is evaluated using the kinetic method,^[8] through a measurement that depends on the difference in the free energy of activation for dissociation to generate the diastereomeric complexes $([\text{Cu}^{\text{II}}(A_R)(\text{ref}^*) - \text{H}]^+ \text{ and } [\text{Cu}^{\text{II}}(A_S)(\text{ref}^*) - \text{H}]^+)$. The kinetic method can discriminate between processes with very small differences (approximately 1 kJ mol^{-1}) in the product ion energy. Competitive dissociation channels of a cluster ion with very small differences in free energy result in large changes in the respective rate constants, which are reflected in the abundances of the fragment ion.^[8] This is a result of the logarithmic relationship between relative ion abundances and the free energy for

dissociation that characterizes this method. A free-energy diagram for the dissociation of cluster ions $[\text{Cu}^{\text{II}}(A_R)(\text{ref}^*)_2 - \text{H}]^+$ and $[\text{Cu}^{\text{II}}(A_S)(\text{ref}^*)_2 - \text{H}]^+$ is shown in Figure 1. Note that the examination of trimeric cluster ions $[\text{Cu}^{\text{II}}(A_R)(\text{ref}^*)_2 - \text{H}]^+$ and $[\text{Cu}^{\text{II}}(A_S)(\text{ref}^*)_2 - \text{H}]^+$ (three chiral ligands in one complex, one mole of the analyte, and two moles of the reference compound) is required so that dissociation can yield the diastereomeric fragment ions $[\text{Cu}^{\text{II}}(A_R)(\text{ref}^*) - \text{H}]^+$ and

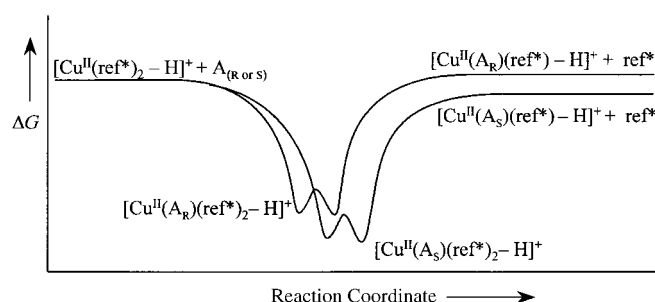


Figure 1. Free-energy diagram for the dissociation of cluster ions bound to copper(II) ions showing the competitive dissociations of two deprotonated trimeric cluster ions that differ in the chirality of one ligand. The two cluster ions yield identical products by one fragmentation route and diastereomeric product ions by a fragmentation process in which a competitive ligand is lost.

$[\text{Cu}^{\text{II}}(A_S)(\text{ref}^*) - \text{H}]^+$, respectively. Under the circumstances just described, one can measure the selectivity to chiral recognition by a chiral selectivity factor R_{chiral} , which is the ratio of the individual ratios of fragment ion abundances when pure enantiomers (A_R and A_S) are applied [Eq. (2)].

$$R_{\text{chiral}} = R_R/R_S = \frac{k_R/k_{\text{ref}^*(1)}}{k_S/k_{\text{ref}^*(2)}} = \frac{[\text{Cu}^{\text{II}}(A_R)(\text{ref}^*) - \text{H}]^+ / [\text{Cu}^{\text{II}}(\text{ref}^*)_2 - \text{H}]^+}{[\text{Cu}^{\text{II}}(A_S)(\text{ref}^*) - \text{H}]^+ / [\text{Cu}^{\text{II}}(\text{ref}^*)_2 - \text{H}]^+} \quad (2)$$

In an initial diagnostic study of the formation of singly charged Cu^{II} -bound cluster ions we chose the complex $[\text{Cu}^{\text{II}}(\text{Ala-L-Ala})_2(\text{Phe}) - \text{H}]^+$ (Phe is L- or D-phenylalanine) as the model ion. To facilitate data interpretation, deuterium-

labeled L-phenylalanine was employed. (Note that only in this diagnostic study was isotopically labeled analyte used. The remaining experiments are performed without using isotopically labeled compounds, which is also one of the advantages of this chiral analysis method.) The relative abundance of $[\text{Cu}^{\text{II}}(\text{A})(\text{ref}^*) - \text{H}]^+$ cluster ions in the mass spectrum depends on the configuration of A, for example, the ratio of relative abundance of $[\text{Cu}^{\text{II}}([\text{D}_5]\text{L-Phe})(\text{Gly-L-Ala}) - \text{H}]^+ / [\text{Cu}^{\text{II}}(\text{L-Phe})(\text{Gly-L-Ala}) - \text{H}]^+$ is approximately 1.8 when an equimolar mixture of D-Phe and $[\text{D}_5]\text{L-Phe}$ is used in solution. Remarkably, the relative abundance of the cluster ions $[\text{Cu}^{\text{II}}([\text{D}_5]\text{L-Phe})(\text{Gly-L-Ala})_2 - \text{H}]^+$ and $[\text{Cu}^{\text{II}}(\text{D-Phe})(\text{Gly-L-Ala})_2 - \text{H}]^+$ varies linearly with the enantiomeric composition of phenylalanine in solution. Similar results were observed when L-tryptophan was employed as the chiral reference.^[9] The abundance of the trimeric ions are reproducibly equal, while the relative abundance ratio of the dimeric ions varies with experimental conditions. The differential formation of dimeric ions may be the result of chiral discrimination, and indeed this experiment is the basis being used by several groups to conduct chiral studies using single-stage mass spectrometry. The present observation suggests that such effects arise from instrumental factors as well as the chemical effects of interest. In contrast, the use of branching ratios in a tandem mass spectrum is a more reliable and reproducible approach. The reason why the formation of cluster ions $[\text{Cu}^{\text{II}}(\text{A}_R)(\text{ref}^*)_2 - \text{H}]^+$ and $[\text{Cu}^{\text{II}}(\text{A}_S)(\text{ref}^*)_2 - \text{H}]^+$ is independent of stereochemistry is still under investigation.

Six dipeptides (Gly-Ala, Ala-Gly, Ala-Ala, Ala-Leu, Leu-Ala, and Ala-Phe) were selected for chiral analysis. The choice of appropriate chiral references was based in part on their abilities to produce large chiral interactions. Aromatic amino acids are favored since they are known to facilitate chiral distinction.^[10] A second factor is structural similarity to the analyte, since this allows the ready formation of a complex. It also allows accurate measurements of relative abundance ratios, otherwise dissociation proceeds overwhelmingly to the more stable product. Typical tandem mass spectra showing the distinction of L-Ala-Gly and D-Ala-Gly using L-tryptophan are illustrated in Figure 2 and chiral recognition of all six dipeptides is summarized in Table 1. Repeat injections were found to give standard deviations of less than 3%. Chiral dipeptides Gly-Ala and Ala-Gly, each bearing one chiral center, are readily distinguished using L-tryptophan as the reference. The rest of the peptides have two chiral centers and are distinguished by R_{chiral} values of at least 1.4. Differentiation of regioisomers and diastereomers is also achieved using this method, but beyond the scope of this paper.

Quantification was performed using the enantiomerically pure chiral reference and the analyte in various optical purities. Two representative systems with moderate chiral selectivity were selected: 1) Gly-Ala as the analyte and L-tryptophan as the reference and 2) Ala-Ala (a mixture of L-Ala-L-Ala and D-Ala-D-Ala) as the analyte and L-tryptophan as the reference. The ratio R of the two fragment ions was measured in a single tandem (MS/MS) spectrum as a function of the optical purity of the analyte. As illustrated in Figure 3, linear relationships of $\ln R$ versus ee values were obtained and

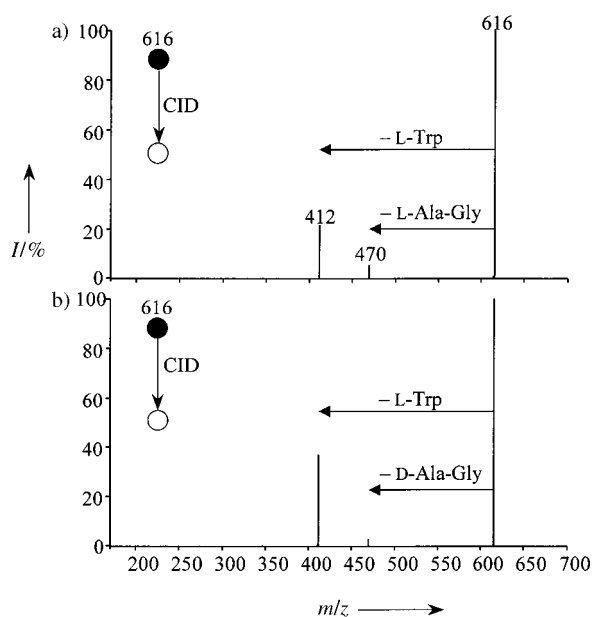


Figure 2. MS/MS product ion spectra of a) $[\text{Cu}^{\text{II}}(\text{L-Ala-Gly})(\text{L-Trp})_2 - \text{H}]^+$ (m/z 616); b) $[\text{Cu}^{\text{II}}(\text{D-Ala-Gly})(\text{L-Trp})_2 - \text{H}]^+$ (m/z 616). The CID activation level chosen (10.5 %) corresponds to approximately 263 mV AC. I refers to the relative ion abundance. No other fragment ions of more than 1 % relative abundance were observed.

Table 1. Chiral recognition of chiral peptides.^[a]

A	Ref ^[b]	$[\text{Cu}^{\text{II}}(\text{ref}^*)(\text{A}) - \text{H}]^+ / [\text{Cu}^{\text{II}}(\text{ref}^*)_2 - \text{H}]^+$	R_{chiral}
Gly-L-Ala	L-Trp	14.3	0.427
Gly-D-Ala	L-Trp	6.10	
L-Ala-Gly	L-Trp	4.51	3.37
D-Ala-Gly	L-Trp	15.2	
L-Ala-L-Ala	L-Trp	22.3	1.50
D-Ala-D-Ala	L-Trp	33.4	
D-Ala-L-Ala	L-Trp	73.00	6.22
L-Ala-D-Ala	L-Trp	11.7	
D-Ala-D-Leu	N-Me-L-Trp	13.2	1.39
L-Ala-L-Leu	N-Me-L-Trp	9.50	
D-Leu-D-Ala	N-Me-L-Trp	45.2	1.75
L-Leu-L-Ala	N-Me-L-Trp	25.8	
D-Ala-L-Phe	L-Phe-L-Tyr	0.0331	3.14
L-Ala-D-Phe	L-Phe-L-Tyr	0.104	
L-Ala-L-Phe	L-Phe-L-Tyr	0.0658 ^[c]	

[a] The CID activation level is optimized in each experiment and then kept constant for the measurements of enantiomers. [b] See text for the criterion on the selection of the reference compound (ref^{*}). [c] The value is not applied to the measurement of chiral selectivity since L-Ala-L-Phe is the epimer of D-Ala-L-Phe or L-Ala-D-Phe.

they showed correlation coefficients (r^2) of 0.9920 for the quantification of Gly-Ala and 0.9936 for the quantification of Ala-Ala enantiomeric mixtures. Note that the linear correlation between the logarithm of the fragment ion abundance ratio and the enantiomeric excess is intrinsic to the kinetic method. According to the kinetic method, $\ln R$ is linearly proportional to $\Delta(\Delta G)$ [Eq. (3)],

$$\ln R = \frac{\Delta(\Delta G)}{RT_{\text{eff}}} \quad (3)$$

where R in the denominator is the gas constant, T_{eff} is the effective temperature of the activated trimeric cluster ion, and

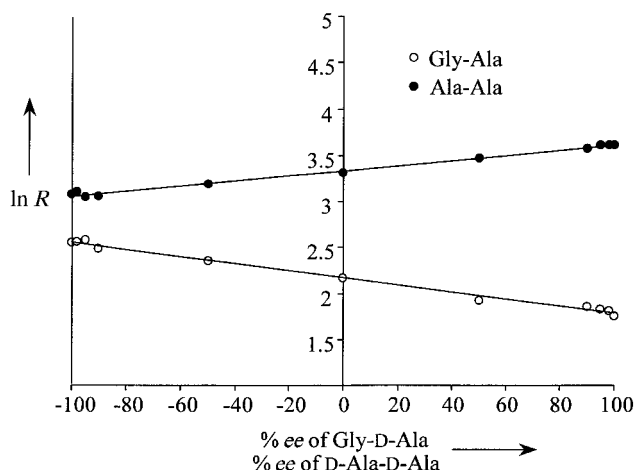
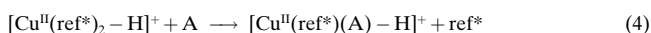


Figure 3. Calibration curves for chiral analysis of Gly-Ala (enantiomeric mixture of Gly-D-Ala and Gly-L-Ala) and Ala-Ala (enantiomeric mixture of D-Ala-D-Ala and L-Ala-L-Ala) using L-Trp as the chiral reference.

$\Delta(\Delta G)$ is defined as the difference in free energies for Equation (4).



The quantity $\Delta(\Delta G)$ is linearly proportional to the enantiomeric excess of the analyte A, therefore $\ln R$ changes linearly with ee . A derivation based on the bond energy instead of free-energy formalism is given elsewhere.^[10] Calibration can be performed with an experimentally established semi-log plot using only a racemic sample and a sample of known enantiomeric excess for each analyte (a two-point calibration). Quantitative chiral analysis is then carried out by measuring the ratio of two fragment ions in a single spectrum in just a minute. For example, Gly-Ala is analyzed to give an accuracy of 3.6% ee over the range 2–100% ee .^[11]

The method for gas-phase chiral quantification reported here has several distinctive features: a) Since chiral selectivity in the gas phase is usually low, the proposed method using parallel reactions is especially attractive for gas-phase chiral quantification of samples with small ee values. b) The method does not rely on condensed-phase derivatization or chromatographic separation, and therefore may be particularly useful for cases in which chromatography and derivatization is ineffective or inconvenient. c) The analysis time is short and does not involve wet-lab steps or chromatographic process. d) The measurements are simple, rapid, and amenable to automation: they use standard ESI mass spectrometry and tandem mass spectrometry, and require very small amounts of sample for analysis. e) The present parallel reaction methodology is general and should be useful for quantification of other biologically important compounds, such as chiral drugs. The experiments are not restricted to copper(II) ions or any particular metal ion complexes, other chiral interactions such as host–guest interactions are possible. The approach used here therefore serves as a possible basis on which to build a general procedure for molecular recognition and chiral analysis in the gas phase.

Experimental Section

A commercial LCQ ion trap mass spectrometer (Finnigan, San Jose, CA), equipped with an ESI source was operated in the positive ion mode as follows: spray voltage: 5.00 kV; capillary voltage: 3 V; heated capillary temperature: 150 °C; tube lens offset voltage: 20 V; sheath gas (N_2) flow rate: 30 units (roughly 0.75 L min⁻¹). The spectra shown represent the average of about 50 scans, each requiring 200 ms. The sample was infused by a syringe pump at a flow rate of 1–3 $\mu\text{L min}^{-1}$. In the full scan MS² and MS³ modes, the parent ion of interest was first isolated by applying an appropriate waveform across the endcap electrodes of the ion trap to resonantly eject all trapped ions, except those with the m/z ratio of interest. The isolated ions were then subjected to a supplementary AC signal to resonantly excite them and so cause CID. The Mathieu q_z values for resonance excitation and resonance ejection were 0.25 and 0.83, respectively. The ion excitation time for CID (values range from 0 to 100% relative collision energy corresponding to 0 to 2.5 V zero-to-peak resonant excitation potential) was 30 ms with the amplitude of the excitation AC being optimized in each experiment, but being kept constant for the measurements of R and S enantiomers.

Gas phase Cu^{II} complexes with dipeptides or amino acids were generated by electrospraying solutions containing a mixture of dipeptides and amino acids (100 μM each) and copper(II) chloride (25 μM) in water/methanol (50/50). Dipeptides and amino acids were purchased from Bachem (Torrance, CA) and Sigma (St. Louis, MO) and were used without further purification.

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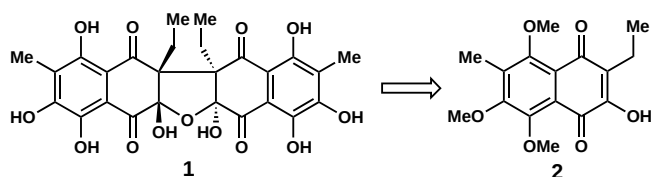
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Total Synthesis of Hybocarpone**

K. C. Nicolaou* and David Gray

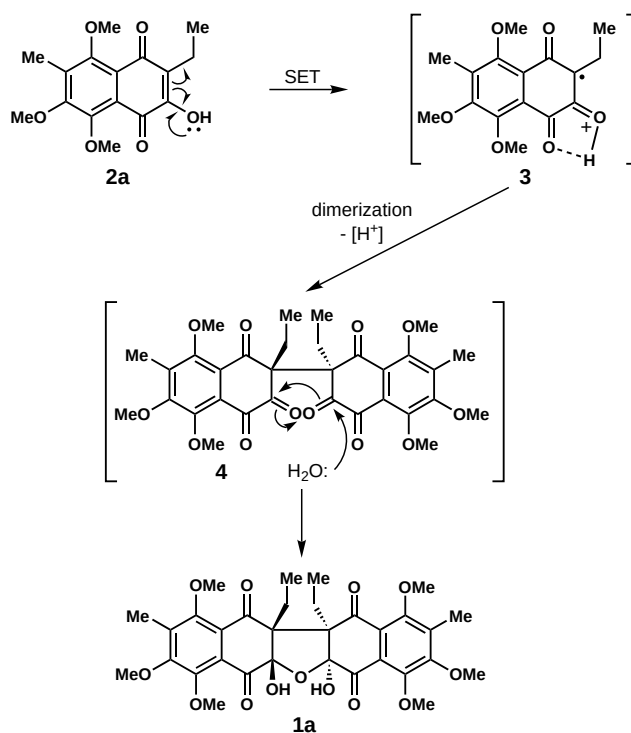
A recent report^[1] disclosed the isolation and structural elucidation of a novel naphthazarin-related natural product with a unique and unprecedented molecular architecture containing a dinaphtho[2,3-*b*:2,3-*d*]furan–tetraone skeleton. Termed hybocarpone (**1**, Scheme 1), this naturally occurring



Scheme 1. Structures of hybocarpone (**1**) and its postulated precursor, naphthazarin **2**.

substance was produced by mycobiont cultures derived from the lichen *Lecanora hybocarpa* and exhibited potent cytotoxic properties against the murine mastocytoma P815 cell line (IC_{50} value 0.15 mg mL^{-1}).^[1] Intrigued by the unique molecular structure and important biological activity of hybocarpone (**1**), we initiated a program directed towards its chemical synthesis. Herein we describe a short total synthesis of racemic **1** based on a dimerization–hydration cascade strategy that may bear resemblance to its biogenetic origins.

The C_2 -symmetric structure of hybocarpone (**1**) renders itself to an aesthetically pleasing retro dimerization disconnection, whereby naphthazarin **2** (Scheme 1) becomes a possible precursor. Crucial to the success of a synthetic strategy based on this premise are: 1) the construction of the highly hindered central carbon–carbon bond and 2) the setting of the relative configuration of the four stereogenic centers of **1** during the assembly process. A viable scenario for the dimerization of **2a** to **1a**, the hexamethylated derivative of **1**, is shown in Scheme 2. Thus, it was postulated that activation of a protected form of **2** (compound **2a**) via a single-electron transfer (SET) process could lead to the highly reactive cation radical species **3**, which may suffer dimerization and proton loss to afford the bridged system **4**. Spontaneous and selective hydration of the hexaketone intermediate **4**, as shown in



Scheme 2. Postulated dimerization–hydration cascade of naphthazarin **2a** to hybocarpone hexamethyl ether (**1a**) initiated by single-electron transfer (SET).

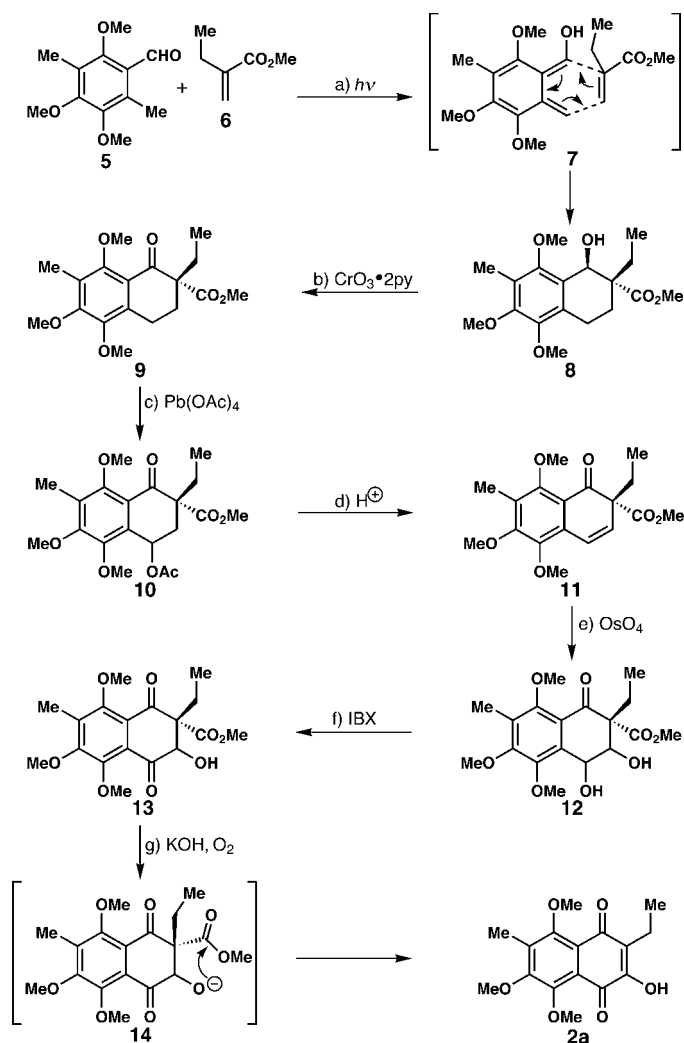
Scheme 2, could then furnish the desired hybocarpone framework **1a**. Only demethylation separates the latter compound from hybocarpone (**1**). The attractiveness of this simple and potentially economical strategy prompted a swift attempt at its laboratory execution.

In pursuing the total synthesis of **1** according to the above dimerization strategy, our first goal was defined as the construction of naphthazarin **2a** (Scheme 2), a monomeric species resembling previously isolated natural products.^[2] Scheme 3 summarizes the synthesis of **2a**. Thus, the known aromatic aldehyde **5**^[3] was irradiated with UV light in toluene in the presence of methyl 2-ethylacrylate (**6**),^[4] furnishing the fused bicyclic system **8** (via the presumed intermediacy of the orthoquinodimethane **7**) in 82 % yield.^[5] Oxidation of the hydroxy group of **8** with $CrO_3 \cdot 2py$ in methylene chloride afforded ketone **9** (86 % yield), which underwent selective acetoxylation with $Pb(OAc)_4$ under UV light irradiation, leading to acetate **10** in 71 % yield. Exposure of **10** to HCl in AcOH at $70^\circ C$ gave olefin **11** in 72 % yield, which was subjected to dihydroxylation with NMO/ OsO_4 to afford the *vic*-diol **12** (92 % yield, ca. 10:1 ratio of diastereomers, unassigned configuration). IBX oxidation of **12** led, chemoselectively, to hydroxyketone **13** (92 % yield) which was treated with KOH in aqueous THF in the presence of air to afford, through a decarboxylation–oxidation sequence, the desired naphthazarin **2a** in 87 % yield. The unusual rapidity of the last reaction suggests neighboring group participation in the ester hydrolysis step as indicated in structure **14**.

With naphthazarin **2a** at hand, we proceeded to investigate its dimerization through the proposed (Scheme 2) radical-

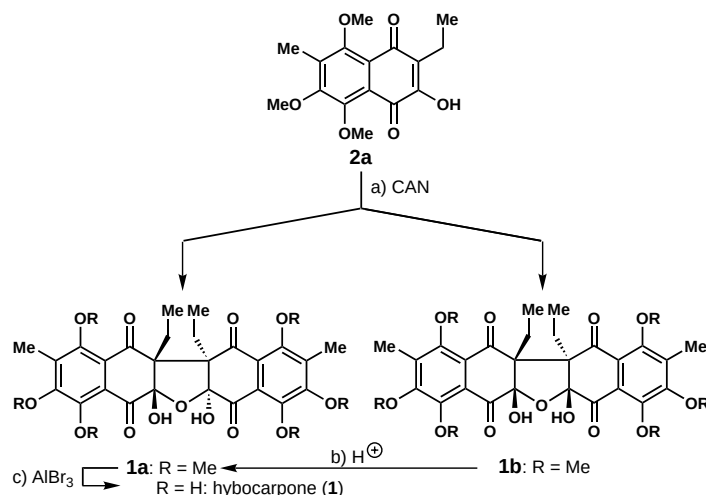
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Scheme 3. Synthesis of naphthazarin **2a**. Reagents and conditions: a) **6** (4.0 equiv), $h\nu$, toluene, 2 h, 82%; b) $\text{CrO}_3 \cdot 2\text{py}$ (8.0 equiv), CH_2Cl_2 , 0 $\rightarrow$ 25 $^\circ\text{C}$, 1 h, 86%; c) $\text{Pb}(\text{OAc})_4$ (1.4 equiv), $h\nu$, AcOH, 2 h, 71%; d) aqueous HCl, AcOH, 70 $^\circ\text{C}$, 30 min, 72%; e) OsO_4 (0.1 equiv), NMO (3.0 equiv), THF/*t*-BuOH/ H_2O /py (20:20:4:1), 12 h, 92%; f) IBX (3.0 equiv), DMSO, 20 $^\circ\text{C}$, 1 h, 92%; g) 1M KOH, H_2O /THF (3:1), air, 1 h, 87%. IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, NMO = *N*-methylmorpholine *N*-oxide.

based mechanism. A search for suitable SET reagents led to the identification of CAN as an inducer of the desired coupling reaction, leading directly to a mixture of two isomeric hybocarpone derivatives **1a** and **1b** (ca. 3:2 ratio, 36% combined yield based on 60% recovered starting material; Scheme 4), which were chromatographically separated and spectroscopically characterized (see Table 1). Interestingly, the more complex ^1H NMR spectrum (CDCl_3 , 500 MHz) of the minor product **1b** was observed to undergo simplification as this apparently unfavorable isomer was transformed to the thermodynamically more stable isomer **1a**. The same transformation was observed when **1b** was exposed to AcOH in CHCl_3 (**1b** $\rightarrow$ **1a**, >95%). This acid-catalyzed transformation also confirmed the *trans* relationship of the two ethyl groups at the junction joining the two monomeric units of both isomers, an outcome predictable on the basis of severe steric congestion within the *cis* isomer.



Scheme 4. Final steps of the total synthesis of hybocarpone (**1**). Reagents and conditions: a) CAN (1.0 equiv), degassed acetonitrile, then **2** in acetonitrile, $-35 \rightarrow 0$ $^\circ\text{C}$, 3 min; then 5M aqueous KOH, 0 $\rightarrow$ 25 $^\circ\text{C}$, 10 min, 36% based on 60% recovered starting material, **1a:1b** (ca. 3:2); b) CDCl_3 , 48 h; or AcOH, 10 min, >95%; c) AlBr_3 (1M in CH_2Br_2 , 28 equiv), EtSH/ CH_2Cl_2 (1:1.5), 0 $^\circ\text{C}$, 1 h, 60%. CAN = ceric ammonium nitrate.

Table 1. Selected data for compounds **2a**, **1a**, and **1**.

2a : yellow solid; R_f = 0.3 (silica gel, hexane/EtOAc 2:1 with 1% AcOH); m.p. 106–108 $^\circ\text{C}$ (CH_2Cl_2); IR (film) $\tilde{\nu}_{\text{max}}$ = 3351, 2928, 1646, 1460, 1402, 1351, 1285, 1127 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 7.39 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 2.57 (q, J = 7.7 Hz, 2H), 2.28 (s, 3H), 1.13 (t, J = 7.7 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 184.1, 180.8, 157.5, 156.6, 152.0, 151.1, 137.3, 125.6, 121.9, 121.6, 61.6, 61.5, 61.2, 17.2, 13.0, 10.4; HR-MS (MALDI): calcd for $\text{C}_{16}\text{H}_{19}\text{O}_6^+$ [$M+\text{H}^+$] 307.1176, found 307.1181
1a : colorless solid; R_f = 0.15 (silica gel, hexane/EtOAc 2:1); m.p. 210–212 $^\circ\text{C}$ (CH_2Cl_2); IR (film) $\tilde{\nu}_{\text{max}}$ = 3388, 2938, 1690, 1559, 1462, 1322, 1117, 1036 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz): δ = 5.11 (s, 2H), 3.95 (s, 6H), 3.92 (s, 6H), 3.81 (s, 6H), 2.36 (dq, J = 12.8, 7.4 Hz, 2H), 2.31 (s, 6H), 1.88 (dq, J = 12.8, 7.4 Hz, 2H), 0.59 (t, J = 7.4 Hz, 6H); ^{13}C NMR (CDCl_3 , 150 MHz): δ = 192.9, 192.0, 157.8, 155.9, 149.4, 136.6, 128.1, 123.8, 101.84, 70.0, 62.7, 62.1, 61.6, 26.5, 11.1, 10.5; HR-MS (MALDI): calcd for $\text{C}_{32}\text{H}_{36}\text{O}_{13}$ [$M+\text{Na}^+$] 651.2048, found 651.2041
1 : orange prisms; m.p. 169–170 $^\circ\text{C}$ (EtOH/ H_2O) (ref. [1]; m.p. 167–168 $^\circ\text{C}$); HPLC: t_{ret} = 23.3 min (0 $\rightarrow$ 100% acetonitrile in water (1% trifluoroacetic acid) over 30 min, 3.5 mL min $^{-1}$, VYDAC C18-reverse-phase column); IR (KBr) $\tilde{\nu}_{\text{max}}$ = 3442, 2965, 1650, 1634, 1595, 1460, 1440, 1362, 1282, 1207, 1134, 1074, 1040, 1012 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz): δ = 13.13 (s, 2H), 10.96 (s, 2H), 6.43 (brs, 2H), 4.79 (s, 2H), 2.63 (dq, J = 14.9, 7.3 Hz, 2H), 2.33 (dq, J = 14.9, 7.3 Hz, 2H), 2.28 (s, 6H), 0.68 (t, J = 7.3 Hz, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 198.5, 193.4, 157.8, 150.2, 143.5, 123.3, 108.6, 107.7, 99.5, 67.3, 25.2, 10.5, 8.9; HR-MS (MALDI): calcd for $\text{C}_{26}\text{H}_{25}\text{O}_{13}^-$ [$M-\text{H}^-$] 543.1144, found 543.1154

Molecular mechanics calculations on all six possible diastereomers of the hybocarpone skeleton revealed that, indeed, **1a** was the thermodynamically most stable (in terms of strain energy) isomer. The generation of hybocarpone (**1**) from its hexamethylated derivative **1a** was effected by exposure to $\text{AlBr}_3/\text{EtSH}$ in methylene chloride at 0 $^\circ\text{C}$ (60% yield). Synthetic **1** exhibited identical spectral data (^1H and ^{13}C NMR) to those reported for natural hybocarpone.^[1, 6]

In conclusion, an expedient strategy for the construction of the hybocarpone (**1**) molecular architecture has been devised and executed, producing the title compound in racemic form. This radical-based dimerization approach, or a closely related

variant of it, may not be too dissimilar to the pathway adopted by nature in the biosynthesis of this natural product. Studies to further elucidate the mechanism of the postulated oxidative dimerization process and the application of the developed chemistry to the construction and biological evaluation of hybocarpone libraries are in progress.

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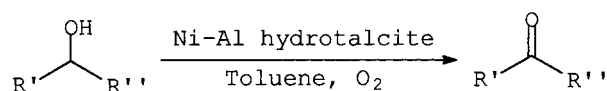
The First Example of Activation of Molecular Oxygen by Nickel in Ni-Al Hydrotalcite: A Novel Protocol for the Selective Oxidation of Alcohols**

B. M. Choudary,* M. Lakshmi Kantam, Ateeq Rahman, Ch. Venkat Reddy, and K. Koteswara Rao

The oxidation of α -ketols as well as allylic and benzylic alcohols to a carbonyl functionality is the foundation of many important current industrial and fine-chemical processes. Several methods are available to effect this conversion and continuous attention is drawn to newer and selective methods of oxidation.^[1] Catalytic oxidation with molecular oxygen is particularly attractive from an economical and environmental point of view.^[2] The oxidation of alcohols employing molec-

ular oxygen requires co-oxidants such as aldehydes, *N*-hydroxyphthalimide, diethyl azodicarboxylate, hydroquinone, or nitrosonium ions to accomplish the catalytic cycle with catalysts based on Ru and Co,^[3] Cu,^[4] and Zr,^[5] while molecular oxygen as the sole oxidant is sufficient when catalysts based on Pt,^[6] Rh,^[7] Pd,^[8] Ru,^[9] Co,^[10] V,^[11] and Os^[12] are used. To the best of our knowledge no report is available in the literature in regard to the activation of molecular oxygen by a nickel catalyst.

The use of heterogeneous catalysts in the liquid phase offers several advantages over homogeneous ones, such as ease of recovery and recycling, atom utility, and enhanced stability in the oxidation of alcohols. Layered double hydroxides (LDHs) or hydrotalcite-like compounds (HTLCs) have recently received much attention as basic catalysts.^[11] We report herein the first direct activation of molecular oxygen by nickel in Ni-Al hydrotalcite as demonstrated by the selective oxidation of various kinds of α -ketols as well as benzylic and allylic alcohols (Scheme 1) at atmospheric pressure. Incidentally, this is also the first report of the selective oxidation of α -ketols by a solid oxidant catalyst.



Scheme 1. Oxidation of allylic and benzylic alcohols in the presence of molecular oxygen.

In order to identify and develop the best Ni catalyst for the activation of molecular oxygen, a study on various hydrotalcite catalysts of different Ni:Al ratios (prepared^[12] by different coprecipitation agents) and Ni: γ -Al₂O₃ in the oxidation of 4-nitrobenzyl alcohol with molecular oxygen was undertaken (Table 1). A series of hydrotalcites containing different ratios of Ni:Al, such as 2:1, 2.5:1, and 3:1, were screened and cat. **A** (Ni:Al 2:1) was found to be the most active. The calcined and rehydrated forms of the hydrotalcite cat. **A** were further evaluated in the oxidation reactions. The activity of the calcined catalyst was considerably reduced, whereas the activity was slightly lowered on rehydration. Hydrotalcite cat. **B** (Ni:Al 2:1) was prepared by an ammonia

Table 1. Oxidation of 4-nitrobenzyl alcohol by different nickel catalysts using molecular oxygen.^[a]

Entry	Catalyst	Time [h]	Yield [%] ^[b]	Specific activity [mmol g ⁻¹ h ⁻¹] ^[c]
1	Ni-Al HTLC (2:1, cat. A)	6	98	0.65
2	Ni-Al HTLC (2:1, rehydrated)	6	80	0.53
3	Ni-Al HTLC (2.5:1)	6	78	0.51
4	Ni-Al HTLC (3:1)	6	37	0.24
5	Ni-Al HTLC (2:1, calcined)	21	58	0.11
6	Ni-Al (cat. B)	20	47	0.09
7	Ni: γ -Al ₂ O ₃ (2 %)	20	no reaction	–
8	Ni: γ -Al ₂ O ₃ (5 %)	20	no reaction	–
9	Ni: γ -Al ₂ O ₃ (10 %)	20	no reaction	–

[a] All reactions were performed with 2 mmol of substrate in 10 mL of toluene using 0.5 g of catalyst under oxygen at 90 °C in the specified time. [b] Yields after column chromatography. [c] Specific activity: mmol of product obtained per gram of catalyst per hour.

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coprecipitation method and showed moderate activity. There was practically no reaction when the Ni: γ -Al₂O₃ catalyst with different compositions was used. Therefore, it is concluded that Ni-Al hydrotalcite cat. **A** was the best catalyst for an effective oxidation of 4-nitrobenzyl alcohol.

The effect of the organic solvents on the oxidation was examined by choosing 4-nitrobenzyl alcohol as the model substrate. Very little oxidation product was obtained with polar solvents such as acetonitrile and methanol (29 and 5% yields, respectively), while nonpolar solvents such as benzene, hexane, cyclohexane, and toluene led to 4-nitrobenzaldehyde in yields of 66, 86, 66, and 98%, respectively, in 6 h. The optimum temperature for the oxidation reaction was 90 °C, and further increase of temperature had no positive effect on the rate of the reaction.

Catalyst **A**, proved to be the best catalyst in our studies, and was further evaluated for the oxidation of various kinds of α -ketols, as well as benzylic and allylic alcohols (Table 2) to their corresponding carbonyl compounds using molecular oxygen

Table 2. The oxidation of various alcohols by Ni-Al hydrotalcite (Ni:Al 2:1, cat. **A**) using molecular oxygen.

Entry	R'	R''	Time [h]	Yield [%] ^[a]
1	C ₆ H ₅	H	12	31
2	<i>m</i> -MeOC ₆ H ₅	H	2	88
3	<i>o</i> -NO ₂ C ₆ H ₅	H	6	76
4	<i>p</i> -NO ₂ C ₆ H ₅	H	6	98
5	<i>o</i> -MeOC ₆ H ₅	H	1.5	86
6	<i>o</i> -MeC ₆ H ₅	H	6	72
7	<i>m</i> -ClC ₆ H ₅	H	15	63
8	<i>m</i> -PhOC ₆ H ₅	H	10	71
9	<i>p</i> -MeOC ₆ H ₅	H	10	88
10	<i>o</i> -ClC ₆ H ₅	H	10	87
11	<i>p</i> -ClC ₆ H ₅	H	10	73
12	<i>o,p</i> -MeOC ₆ H ₅	H	12	88
13	C ₆ H ₅	CH ₃	12	95 (94) ^[b]
14	<i>p</i> -MeOC ₆ H ₅	CH ₃	6	84
15	<i>p</i> -MeC ₆ H ₅	CH ₃	2	96
16	<i>p</i> -NO ₂ C ₆ H ₅	CH ₃	3	92
17	C ₆ H ₅	C ₆ H ₅	1.5	95
18	C ₆ H ₅ CO	C ₆ H ₅	2.5	93
19	C ₆ H ₅	C ₆ H ₅ (OH)CH	1.5	93
20	C ₆ H ₅	CH ₂ CH ₃	7	72
21	C ₆ H ₅ OCO	C ₆ H ₅ O	3	96
22	C ₆ H ₅ CH=CHCH ₂	H	6	88
23	<i>o</i> -NO ₂ C ₆ H ₄ CH=CHCH ₂	H	10	84
24	<i>p</i> -MeOC ₆ H ₄ CH=CHCH ₂	H	10	96
25	<i>p</i> -BrC ₆ H ₄ CH=CHCH ₂	H	12	95

[a] Yields of isolated products. [b] Yield after the 6th cycle.

as the sole oxidant. Although the oxidation of benzyl alcohol (Table 2, entry 1) with cat. **A** is low yielding, the oxidation of other substituted benzyl alcohols (Table 2, entries 2–12) proceeds in excellent yields. It is notable that the benzyl alcohols (Table 2, entries 1–12) are oxidized selectively to their corresponding aldehydes under the reaction conditions used. Secondary benzylic alcohols (Table 2, entries 13–21) are oxidized quantitatively in the present catalytic system at a faster rate than primary ones. This observation is in contrast to the study reported by Kaneda et al., using Ru hydrotalcites,^[9] wherein primary benzylic alcohols were oxidized at a faster

rate. The rate of oxidation of substituted benzyl alcohols, irrespective of the electron-donating or -withdrawing substituent at the aromatic nucleus, is faster than that of benzyl alcohol. It is significant to note that the oxidation of 1-phenylethanol to acetophenone in the presence of air instead of oxygen occurred in 50% yield (12 h), which indicates that the presence of CO₂ present in air had not poisoned the reaction. By using our method it is possible to synthesize α -dicarbonyl compounds, which are useful intermediates in the synthesis of heterocyclic compounds, by the oxidation of α -ketols (Table 2, entries 18, 21). This result is quite impressive, since all the methodologies described earlier for the oxidation of α -ketols generate toxic wastes. Although the recently reported VOCl₃-mediated^[1e] catalytic oxidation of α -ketols produces no toxic wastes, recovery of the catalyst from the reaction medium is difficult. It is significant that the oxidation of α -furoin to α -fural is a quite useful method for the synthesis of α -dicarbonyl compounds in high yields (Table 2, entry 21). The another unique advantage of this method is the one-pot oxidation of vicinal diols to α -dicarbonyl compounds in quantitative yields (Table 2, entry 19). Cinnamyl alcohol and its substituted counterparts (Table 2, entries 22–25) are selectively oxidized to their corresponding α,β -unsaturated aldehydes without affecting the double bond. In addition, the oxidation of the aliphatic primary allyl alcohol, geraniol, provides the corresponding α,β -unsaturated aldehyde selectively in a moderate yield of 46% in 8 h. However, the oxidation of aliphatic primary and secondary alcohols such as 1-decanol and 2-octanol affords the corresponding carbonyl derivatives in low yields (19 and 20%, respectively) in 10 h under these conditions. Furthermore, cat. **A** can be reused for several cycles without loss of its activity and selectivity. No reaction occurred when the reaction was conducted with the filtrate obtained after removal of the solid catalyst after the reaction, which indicates that the active ingredient was not leached out of the solid catalyst. The reused catalyst exhibited a similar hydrotalcite powder X-ray diffraction (XRD) pattern, even after the sixth cycle.

The observed order of the specific activity in the oxidation is: Ni-Al hydrotalcite (cat. **A** as synthesized) > rehydrated Ni-Al hydrotalcite > Ni-Al hydrotalcite (Ni:Al 2.5:1) > Ni-Al hydrotalcite (Ni:Al 3:1) > Ni-Al calcined hydrotalcite > Ni-Al (cat. **B**) >> Ni: γ -Al₂O₃. A temperature-programmed reduction (TPR) profile (Figure 1) of all the catalysts indicates that free NiO is reduced at low temperature (400 °C; T_{max}) and NiO in association with aluminum oxide is reduced at higher temperature (500 °C; T_{max}).^[12c] The TPR of the samples of Ni: γ -Al₂O₃ indicate the presence of free NiO only, while the samples of Ni-Al hydrotalcite prepared by the coprecipitation agents, NaOH/Na₂CO₃, and ammonia display both free NiO and NiO in association with aluminum oxide. The inert nature of Ni: γ -Al₂O₃ in the oxidation of alcohols indicates that free NiO is the inactive species in the oxidation reactions. The activation of molecular oxygen by all the samples of Ni-Al hydrotalcites, as evident by the oxidation of alcohols, is attributed to the presence of Ni in association with aluminum oxide. The TPR profile of Ni-Al hydrotalcites prepared by NaOH/Na₂CO₃ precipitation displayed a shoulder at lower temperature which grows on increased free NiO content,

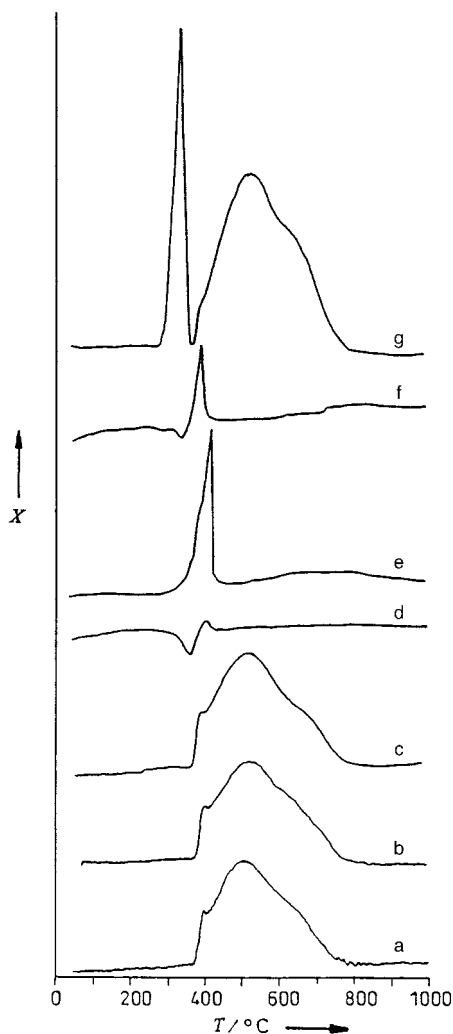


Figure 1. TPR profiles plotted as amount of hydrogen consumed (X in arbitrary units) versus temperature [$^{\circ}\text{C}$] of a) Ni-Al hydrotalcite (cat. **A**), b) Ni-Al hydrotalcite (Ni:Al 2.5:1), c) Ni-Al hydrotalcite (Ni:Al 3:1), d) Ni: γ - Al_2O_3 (2%), e) Ni: γ - Al_2O_3 (5%), f) Ni: γ - Al_2O_3 (10%), g) Ni:Al (cat. **B**).

namely from Ni:Al 2:1 to 3:1, although XRD analysis showed a crystalline hydrotalcite pattern. The rate of oxidation of alcohols, which is in the increasing order: 3:1 < 2.5:1 < 2:1 (Ni:Al), is in good agreement with the TPR data of hydrotalcites. The examination of IR spectra of various compositions of Ni-Al hydrotalcites shows that the vibrational stretching frequency of the hydrogen atom in a hydroxide group of the cat. **A** with a 2:1 Ni:Al ratio appears at lower wavenumber (3420 cm^{-1}) and has a smaller half-width than the other compositions, which indicates there is a more-ordered cation distribution (Figure 2) in the former.^[13] The higher specific activity ($0.65\text{ mmol g}^{-1}\text{ h}^{-1}$) of Ni-Al hydrotalcite (cat. **A**) as synthesized (Table 1, entry 1) is thus attributed to the presence of Brønsted basic hydroxyl groups and also an excellent layered structure that offers access of the reactants to the active sites of the

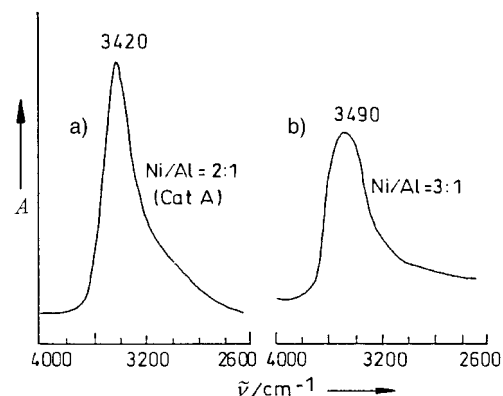
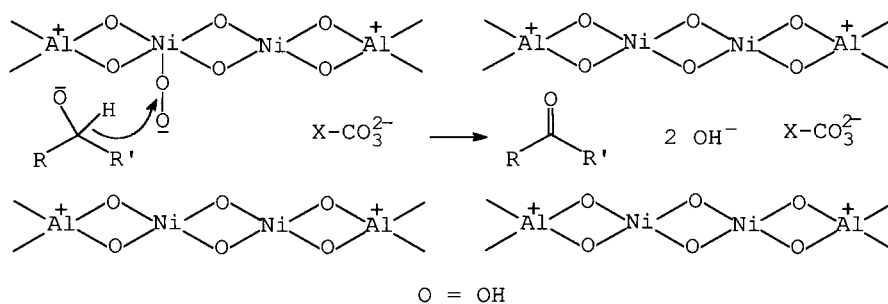


Figure 2. Hydroxy stretching vibrations of a) Ni-Al hydrotalcite, cat. **A** (Ni:Al 2:1) and b) Ni-Al hydrotalcite (Ni:Al 3:1).

catalysts. All these results identify Ni in association with aluminum oxide as the active species for the activation of molecular oxygen.

Further, the higher activity of hydrotalcite cat. **A** as synthesized is also a consequence of the presence of carbonate anion in the interlayers, which is in agreement with the results obtained in the oxidation by Ru hydrotalcite.^[9] The slightly lowered specific activity of $0.53\text{ mmol g}^{-1}\text{ h}^{-1}$ (Table 1, entry 2) obtained upon rehydration of the hydrotalcite cat. **A**, in which inclusion of carbonate anions is precluded, strengthens the assumption that the presence of carbonate anions enhance the activity in the synthesized cat. **A**. Upon calcination, the hydrotalcite cat. **A** displayed considerable reduction in activity as a consequence of the loss of both Brønsted hydroxyl groups and carbonate anions: a result that corroborates the above hypothesis.

A plausible reaction mechanism (Scheme 2), therefore, involves the formation of an alkoxide on interaction of the alcohol with the Brønsted OH group (basic site) of the brucite layer originally present in Ni-Al hydrotalcite. The hydrotalcite further reacts with molecular oxygen to form a peroxide. Hydride transfer then takes place from the alkoxide to the peroxide to generate the carbonyl product, with regeneration of an OH anion of the brucite layer. This in turn reacts with a fresh molecule of alcohol to give alkoxide and initiate another cycle. Aluminum is well documented both in Oppenauer oxidation and Meerwein-Ponndorf-Verley (MPV) reduction, as well as in the recently reported MPV reduction^[11e] of ketones by Mg-Al hydrotalcite, to favor the formation of alkoxide, while the neighboring Ni atom



Scheme 2. Proposed mechanism for the oxidation.

facilitates the formation of a peroxide species with molecular oxygen. The hydride transfer from the aluminum alkoxide of hydrotalcite is effected by the neighboring peroxide on the nickel atom. Hydrotalcites are homogeneous mixtures of heterobimetallic composition having a periodic composition of M^{II} and M^{III} ions. The cationic order of cat. **A** as revealed by IR studies suggests that the presence of one aluminum atom for every two nickel atoms substituted alternately in the hydrotalcite provides the optimum use of nickel in cat. **A**, better than is possible with the other compositions, and is thus responsible for the display of higher activity.

In conclusion, Ni-Al hydrotalcite efficiently oxidizes a wide range of alcohols, such as allylic and benzylic, and α -ketols to the corresponding carbonyl compounds under mild reaction conditions by employing molecular oxygen as the stoichiometric oxidant. This process is not only economically viable but also applicable to large-scale reactions. Moreover, the high yields of oxidized products can be obtained in heterogeneous catalysis using hydrotalcites as catalysts.

Experimental Section

Various catalysts with varied composition of Ni-Al hydrotalcites (Ni:Al = 2:1 (cat. **A**), 2.5:1, 3:1) were prepared by coprecipitation employing NaOH/ Na_2CO_3 as described in the literature.^[12a] Catalyst **A** was rehydrated according to our previous report^[11b] and calcined at 450 °C in a flow of air. Ni-Al hydrotalcite (Ni:Al 2:1, cat. **B**) was prepared by coprecipitation using ammonia solution.^[12b] The samples of nickel impregnated on γ -alumina (2, 5, and 10 %) were prepared by adding the required amounts of $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ in water to γ -alumina and stirring occasionally while heating on a water bath till complete evaporation of water had occurred. The residue was dried in an oven at 110 °C for 16 h.

Typical oxidation procedure: Oxygen was bubbled at atmospheric pressure through a reaction mixture containing *p*-nitrobenzyl alcohol (2 mmol) and catalyst (0.5 g) in toluene (10 mL) at 90 °C under stirring. The reaction was monitored by thin-layer chromatography and purified by column chromatography (hexane:ethyl acetate, 95:5, v:v) to afford the *p*-nitrobenzaldehyde as a pale yellow solid: 0.296 g (98 %), m.p. 105 °C, ^1H NMR (200 MHz, CDCl_3 , 25 °C, TMS): δ = 8.1 (d, $^3J(\text{H,H})$ = 8.3 Hz, 2H, aryl-H), 8.4 (d, $^3J(\text{H,H})$ = 8.3 Hz, 2H, aryl-H), 10.2 (s, 1H, CHO); IR (KBr pellets) $\tilde{\nu}$ = 1700 cm^{-1} (sh, C=O); MS (70 eV) m/z (%): 151 (64) [M^+], 150 (61) [$M^+ - \text{H}$], 105 (20) [$\text{C}_6\text{H}_7\text{O}^+$], 77 (93) [C_6H_5^+], 51 (100) [C_4H_3^+].

TPR profiles were recorded on Micromeritics (Auto Chem 2910) using 0.05 g of the uncalcined sample. The sample was dried at 120 °C in an argon flow and then helium was replaced by a flow of a mixture of 5 % hydrogen in helium at room temperature.

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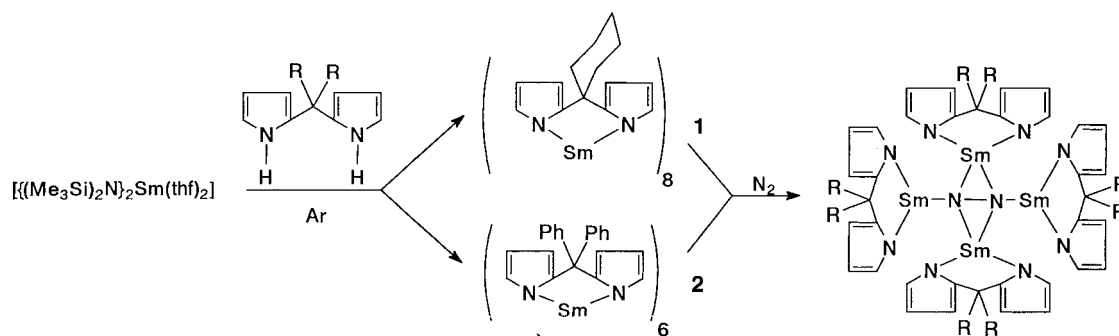
Highly Reactive Sm^{II} Macrocyclic Clusters: Precursors to N_2 Reduction**

Mani Ganesan, Sandro Gambarotta,* and Glenn P. A. Yap

Divalent samarium complexes have been prepared with a wide variety of ligand systems,^[1] but the extreme level of reactivity and the uniqueness of transformations displayed by the samarocene derivatives^[2] was never reproduced. To date, the Sm^{II} polypyrrolide derivatives^[3] are the only systems which share with decamethylsamarocene^[4] the ability to react with an exceedingly inert molecule such as dinitrogen. Unlike samarocene, however, these species may perform *four-electron* reduction of dinitrogen, thus indicating that their reducing power is particularly strong. Particularly versatile with this respect are divalent samarium complexes of dipyrrolide dianions,^[5] which are reminiscent of the ansa-metallocene ligand systems. So far these species have led to three novel dinitrogen complexes.^[6, 7] However, attempts to isolate the presumably highly reactive divalent precursors

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Scheme 1. Synthesis of **1** and **2** and subsequent reaction with N_2 .

analogous to the samarocenes instead yielded rather stable tetra-, penta-, or octanuclear mixed-valence complexes,^[6–8] containing a variety of fragments. This adds further support to the idea that the divalent precursors may be highly reactive. Herein we describe a different synthetic approach that has allowed us to isolate two halogen- and alkali-free Sm^{II} macrocyclic complexes which are rare examples of lanthanide cyclic clusters^[8,9] and the first of this type exclusively containing highly reactive divalent samarium.

Reaction of $[Sm\{N(SiMe_3)_2\}_2(thf)_2]^{[1d]}$ with one equivalent of 1,1-di-(α -pyrrolyl)cyclohexane in THF under an argon atmosphere afforded dark red crystals of the octameric divalent cluster $[\{ [1,1-(\alpha-C_4H_3N)_2C_6H_{10}]Sm \}_8(thf)_4] \cdot \text{hexane}$ (**1**) in very good yield (Scheme 1).

The crystal structure of compound **1** shows that the molecule is composed of eight Sm atoms bridged by eight ligands arranged to form a neutral macrocyclic Sm^{II} complex in which the samarium atoms adopt a flattened boatlike conformation (Figure 1). The coordination of four molecules of THF to four of the eight Sm centers results in two sets of samarium atoms. Each samarium atom without coordinated THF is bridged to the next (with coordinated THF) by one dipyrrolyl dianion; the pyrrole rings in turn are π -bonded to one samarium atom and σ -bonded to a second. As a result, the coordination geometry around each samarium atom is

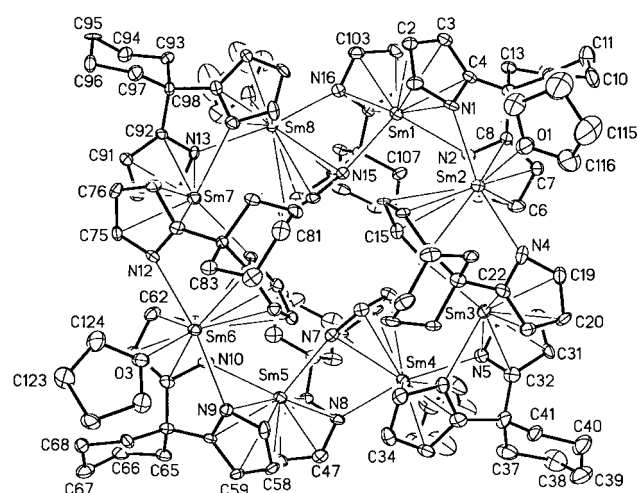


Figure 1. Structure of **1**. Bond lengths [$\text{\AA}$] and angles [$^\circ$]: Sm2–N1 2.588(7), Sm2–O1 2.595(7), Sm2–N4 2.604(8), Sm2–N2 2.812(7), Sm2–N3 2.810(7); N1–Sm2–O1 77.2(2), N1–Sm2–N4 159.9(2), O1–Sm2–N4 82.7(2), N1–Sm2–N2 65.4(2), O1–Sm2–N2 124.7(2), N4–Sm2–N2 128.5(2), N1–Sm2–N3 127.4(2), O1–Sm2–N3 129.8(2), N4–Sm2–N3 66.9(2), N2–Sm2–N3 105.4(2).

strongly reminiscent of that of a bent samarocene with one pyrrolyl ring from each ligand being π -bonded and the two others σ -coordinated. The four Sm atoms bearing one THF molecule display a trigonal-bipyramidal geometry. The centroids of two π -bonded pyrrolyl rings and the oxygen atom of the coordinated THF define the equatorial plane, while the nitrogen atoms of two σ -bonded pyrrolyl rings are at the axial positions.

The analogous reaction carried out with $Ph_2C(\alpha-C_4H_3N)_2H_2$ afforded the hexameric paramagnetic cluster $[[Ph_2C(\alpha-C_4H_3N)_2]Sm \}_6(thf)_3] \cdot (THF)_{6.5}$ (**2**) in 56% yield. In this particular case the six samarium atoms form a regular, flat hexagon with Sm–Sm distances ranging from 4.359 to 4.225 $\text{\AA}$ (Figure 2). The ligand adopts the characteristic bonding mode

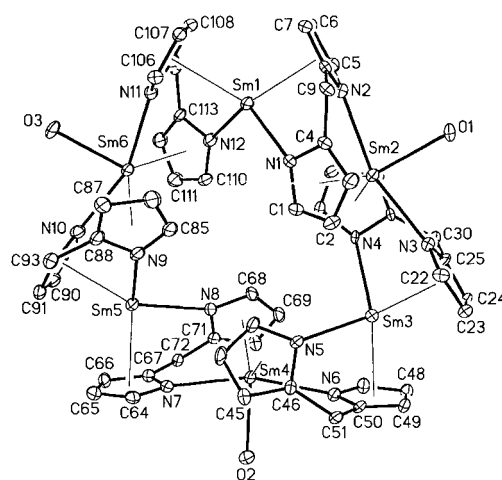


Figure 2. Structure of **2**. Bond lengths [$\text{\AA}$] and angles [$^\circ$]: Sm1–N12 2.656(11), Sm1–N1 2.677(10), Sm1–N2 2.775(10), Sm1–C8 2.780(12), Sm1–N11 2.839(10), Sm2–O1 2.546(8); N12–Sm1–N1 116.6(3), N12–Sm1–N2 124.6(3), N1–Sm1–N2 64.3(3), N12–Sm1–N11 64.5(3), N1–Sm1–N11 124.3(3), N2–Sm1–N11 165.3(3), O1–Sm2–N3 81.1(3), O1–Sm2–N2 80.3(3), N3–Sm2–N2 161.3(3), O1–Sm2–N4 125.5(3), N3–Sm2–N4 63.3(3), N2–Sm2–N4 128.1(3), O1–Sm2–N1 125.0(3), N3–Sm2–N1 129.8(3), N2–Sm2–N1 64.2(3), N4–Sm2–N1 109.5(3).

bridging each pair of metals by crossing σ and π interactions. Again, two sets of samarium atoms are observed: those without coordinated THF, which display the usual bent samarocene-type structures, and those coordinated to THF in which the metal adopts a trigonal-bipyramidal geometry.

Upon exposure to N_2 , solutions of **1** and **2** in THF (Scheme 1) rapidly formed the corresponding previously

reported tetranuclear dinitrogen complexes $[[[R_2C(\alpha-C_4H_3N)_2]Sm]_4 \cdot (THF)_2](\mu-N_2)^{[6,7]}$ in good yield (71 and 75%, respectively). Complex **2** reacts considerably slower than **1** (2 weeks) presumably due to its very poor solubility. Conversely, when the reactions leading to the formation of **1** and **2** were carried out under an N_2 atmosphere, the corresponding dinitrogen complexes were rapidly obtained in good yield (70 and 77%, respectively). The four-electron reduction of dinitrogen and the irreversibility of the fixation sharply contrast with the labile coordination observed with decamethylsamarocene^[4] and calix[4]tetrapyrrole derivatives,^[3b] indicating that compounds **1** and **2** probably are stronger reductants.

The formation of the dinitrogen complex from octameric **1** is a relatively straightforward process in which two molecules of dinitrogen cleave the octameric structure into two tetrameric dinitrogen complexes. Conversely, in the case of **2** the formation of the dinitrogen complex $[[[Ph_2C(\alpha-C_4H_3N)_2]Sm]_4(thf)_2](\mu-N_2)$ implies dissociation of a dimeric $[[[Ph_2C(\alpha-C_4H_3N)_2]Sm]_2(thf)]$ unit and its possible recombination into a second tetrameric unit.

An intriguing question arises about the factors that prevent the complete cleavage of the $N \equiv N$ bond in these two clusters, which are capable of performing both fixation and four-electron reduction of dinitrogen. Both **1** and **2** have available the six-electron pool necessary for the cleavage of the $N \equiv N$ bond. Complex **1** in particular seems to be a perfect candidate for the task. A six-electron reduction of N_2 , hypothetically performed by **1**, would result in the formation of a mixed-valence octameric compound containing two nitrides in the middle of the polymetallic cycle. This type of structure is perfectly stable and was previously observed with the halide-containing mixed-valence octameric complexes.^[8] The fact that the reduction stops at the hydrazido tetraanion stage is even more surprising considering that the cleavage of a $N-N$ single bond requires far less energy (159 kJ mol^{-1}) than the four-electron reduction of N_2 (787 kJ mol^{-1}). This behavior can be explained by assuming that the encapsulation of N_2 into a small tetranuclear cluster is the factor preventing further dinitrogen reduction. In support of this claim, our recent attempts to cleave the residual $N-N$ bond in $[[[1,1'-(\alpha-C_4H_3N)_2C_6H_{10}]Sm]_4 \cdot (THF)_2](\mu-N_2)$ by using a strong reducing agent such as Na, reduced two of the four Sm centers in the process has led to a shortening rather than a lengthening of the $N-N$ distance.^[7]

In conclusion, two unique macrocyclic clusters containing highly reactive divalent samarium atoms were prepared. The bent-metalocene type of structure is probably responsible for the very high reactivity. We are currently investigating the use of these macrocyclic compounds for multiple redox processes aimed at molecular activation.

Experimental Section

1: A solution of $[Sm[N(SiMe_3)_2]_2(thf)_2]$ (1.1 g, 1.9 mmol) in anhydrous THF (40 mL) was treated with 1,1-di-(α -pyrrolyl)cyclohexane (0.4 g, 1.9 mmol) at room temperature under an argon atmosphere. The solution was allowed to stand for 12 h and then concentrated to a small volume (20 mL). The addition of hexane to this solution (10 mL) yielded dark red crystals of **1** (0.7 g, 0.2 mmol, 94% based on Sm) after the mixture had been left to stand

for two days at room temperature. Elemental analysis (%) calcd for $C_{134}H_{174}N_{16}O_4Sm_8$: C 49.13, H 5.35, N 6.84; found: C 48.80, H 5.18, N 6.63; IR (Nujol mull): $\tilde{\nu}$: 3090 (m), 3058 (m), 1422 (s), 1346 (w), 1296 (m), 1272 (m), 1262 (m), 1245 (w), 1233 (w), 1192 (m), 1176 (w), 1155 (s), 1135 (w), 1127 (m), 1092 (m), 1030 (vs), 956 (m), 931 (w), 903 (m), 893 (m), 872 (m), 849 (w), 829 (w), 747 (vs), 631 (s), 575 (m) cm^{-1} ; $\mu_{\text{eff}} = 8.79 \mu_B$ per unit formula.

2: A solution of $[Sm[N(SiMe_3)_2]_2(thf)_2]$ (2.2 g, 3.5 mmol) in THF (40 mL) was treated at room temperature under an argon atmosphere with diphenyl dipyrromethane (1.0 g, 3.5 mmol). The addition of hexane (10 mL) gave dark red crystals of **2** (1.1 g, 0.33 mmol, 56%) after the mixture had been allowed to stand at room temperature for seven days. Elemental analysis (%) calcd for $C_{164}H_{172}N_{12}O_{9.5}Sm_6$: C 58.53, H 5.15, N 4.99; found: C 58.37, H 5.03, N 4.91; IR (Nujol mull): $\tilde{\nu}$: 1371 (w), 1320 (w), 1261 (vs), 1231 (s), 1183 (s), 1150 (vs), 1081 (vs), 1040 (vs), 978 (w), 963 (w), 924 (s), 881 (s), 848 (s), 801 (s), 761 (vs), 742 (vs), 704 (vs), 657 (s), 636 (s), 622 (w), 613 (w) cm^{-1} ; $\mu_{\text{eff}} = 6.81 \mu_B$ per unit formula.

Crystal structure analysis data for **1**: $C_{134}H_{174}N_{16}O_4Sm_8$, $M_r = 3275.69$, triclinic, $P\bar{1}$, $a = 16.703(2)$, $b = 18.150(2)$, $c = 24.750(3)$ Å, $\alpha = 102.839(2)$, $\beta = 100.971(2)$, $\gamma = 99.943(2)^\circ$, $V = 6998.5(15)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.554 \text{ Mg m}^{-3}$; $\mu = 3.352 \text{ mm}^{-1}$, $F(000) = 3236$, 54 903 reflections collected, 27 927 independent reflections, $GOF = 1.018$, $R = 0.0436$, $wR_2 = 0.1038$. Crystal structure analysis data for **2**: $C_{164}H_{172}N_{12}O_{9.5}Sm_6$, $M_r = 3365.24$, triclinic, $P\bar{1}$, $a = 16.549(1)$, $b = 18.918(1)$, $c = 26.187(2)$ Å, $\alpha = 102.973(2)$, $\beta = 103.397(2)$, $\gamma = 109.175(1)^\circ$, $V = 7118.7(9)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.570 \text{ Mg m}^{-3}$; $\mu = 2.499 \text{ mm}^{-1}$, $F(000) = 3376$, 55 952 reflections collected, 14 841 independent reflections, $GOF = 1.072$, $R = 0.0550$, $wR_2 = 0.1143$.

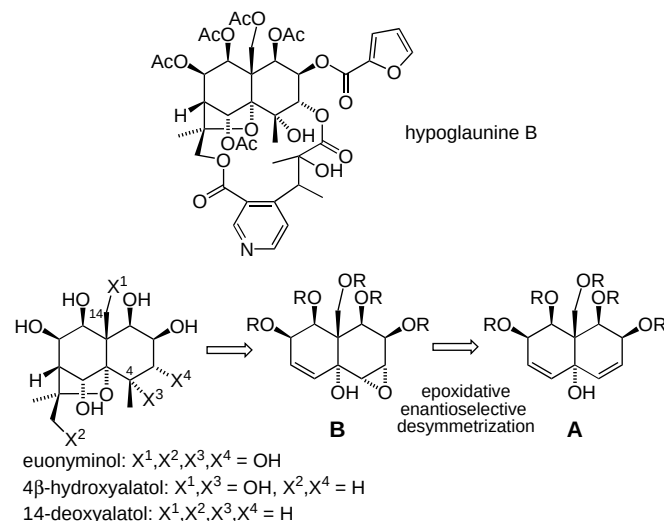
Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-151133 (**1**) and CCDC-151134 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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ularly esters of three polyhydroxylated agarofurans: euonyminol, 4 β -hydroxyalatol, and 14-deoxyalatol, exhibit significant biological activity. These include: triptogelins A-1/A-6^[3a] and celhin A^[3b] (antitumor), wilfortrine^[4] (immunosuppressive), wilforine^[5] (insecticidal), and celangulin^[6a] and cathedulins E-3/E-4/E-5^[6b] (insect antifeedant). Additionally, hypoglaunine B and related macrocyclic lactone derivatives of euonyminol have recently been shown to display significant anti-HIV activity^[7] (Scheme 1).



Scheme 1. Desymmetrization strategy. R = protecting group, Ac = acetyl.

Enantioselective Desymmetrization of *meso*-Decalin Diallylic Alcohols by a New Zr-Based Sharpless AE Process: A Novel Approach to the Asymmetric Synthesis of Polyhydroxylated *Celastraceae* Sesquiterpene Cores**

Alan C. Spivey,* Steven J. Woodhead, Matthew Weston, and Benjamin I. Andrews

Crude plant extracts of the *Celastraceae* have been valued since antiquity for their stimulant, appetite suppressive, antiarthritic, antibacterial, insect repellent, and memory-restorative properties.^[1] Pervasive among the secondary metabolites isolated from this class of plants is a large family of polyhydroxylated sesquiterpene esters having a dihydro- β -agarofuran skeleton.^[2] Many members of this family, partic-

One striking feature of the three core structures common to these natural products is a symmetric array of hydroxyl groups on the top face of their “northern” periphery. We were intrigued by the possibility of exploiting this symmetry to facilitate their synthesis. In particular, we identified epoxide **B** as a pivotal intermediate for the preparation of all the core structures and we envisaged that a two-directional synthesis of *meso*-diallylic alcohol **A** followed by epoxidative enantioselective desymmetrization^[8] would provide an efficient route to this intermediate (Scheme 1). Here we describe how the successful implementation of this plan required the development of a Zr-based Sharpless asymmetric epoxidation (AE) process for tertiary diallylic alcohols.

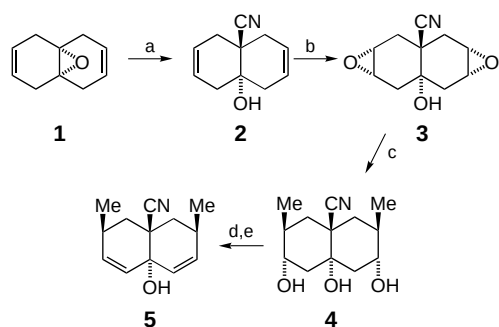
At the outset of our work, only one *trans*-decalinic diallylic alcohol had been reported.^[9] In view of this limited precedent, and the potentially labile nature of the structure, we opted to evaluate the feasibility of our strategy on simple model system **5** (Scheme 2). Epoxide **1** was prepared from naphthalene by Birch reduction (Na/NH_3 ; 74% yield) then epoxidation ($\text{CH}_3\text{CO}_3\text{H}$; 87% yield).^[10] Ring opening with Et_2AlCN ,^[11] followed by completely diastereoselective epoxidation and *trans*-diaxial ring opening with Me_3Al gave triol **4**. Selective mesylation then *anti* elimination in neat DBU furnished the requisite diallylic alcohol **5**. This alcohol was prone to partial [1,3]-allylic rearrangement to give the corresponding conjugated dienyl alcohol on silica, but could be obtained pure after chromatography on grade 1 basic alumina.

Sharpless AE^[12] with either catalytic^[13] or stoichiometric^[13] amounts of $\text{Ti}(\text{OiPr})_4$ -*b*-(-)-diisopropyl tartrate (DIPT) pro-

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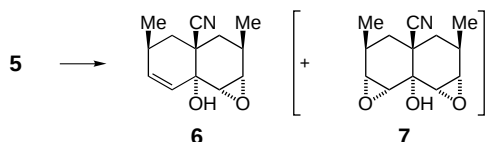
[**] AE = Asymmetric epoxidation. Grateful acknowledgement is made to the EPSRC for a QUOTA studentship (S.J.W.) and to Pfizer (Drs. Alan R. Brown and John P. Mathias) for financial support of this work.

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



Scheme 2. Synthesis of diallylic alcohol **5**. a) Et_2AlCN , CH_2Cl_2 , RT (98%); b) $[\text{VO}(\text{acac})_2]$, $t\text{BuOOH}$, CH_2Cl_2 , 70°C (87%); c) Me_3Al , CH_2Cl_2 , 40°C (88%); d) MsCl , Et_3N , CH_2Cl_2 , RT (81%); e) DBU , 100°C (92%). acac = acetylacetonate, Ms = mesyl = methanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

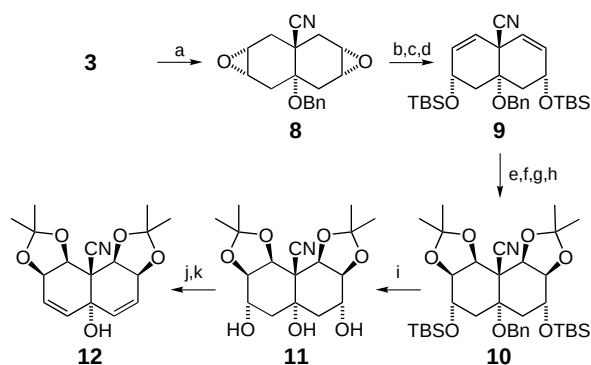
ceeded without detectable [1,3]-allylic rearrangement and afforded epoxy alcohol (–)-**6** in yields up to 70%, but despite extensive experimentation the *ee* value was reproducibly in the range of 10–20% (Scheme 3). Known variations employing other tartrate/tartramide ligands^[14] and/or $\text{CaH}_2/\text{silica}$ ^[15]



Scheme 3. Epoxidation of diallylic alcohol **5**.

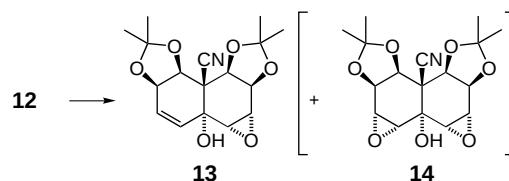
additives failed to improve the situation. Tertiary alcohols are notoriously poor substrates for Sharpless AE because they bind poorly to the tartrate–Ti complex,^[12, 16] so we explored the replacement of $\text{Ti}(\text{O}i\text{Pr})_4$ with $\text{Zr}(\text{O}i\text{Pr})_4$, reasoning that complex formation might be facilitated by the increased Zr–O bond length compared to that of Ti–O.^[17, 18] To our delight we found that use of commercial $\text{Zr}(\text{O}i\text{Pr})_4 \cdot i\text{PrOH}$ (1 equiv),^[19] D-(–)-DIPT (1.1 equiv), and $t\text{BuOOH}$ (1.2 equiv) in CH_2Cl_2 at -20°C for 3 days afforded epoxy alcohol (+)-**6**, in 76% yield and 92% *ee*. An analogous reaction with L-(+)-DIPT afforded (–)-**6** in 90% yield and 92% *ee*.^[20]

Our efforts then turned to the preparation of a fully functionalized decalin (see **A**, Scheme 1). The synthesis of such a compound, wherein the C-14 hydroxymethyl group (product numbering) is protected as a nitrile, is outlined in Scheme 4. Thus, protection of the tertiary hydroxyl group of bis-epoxide **3** as the benzyl ether allowed for a completely diastereoselective three-step conversion into the corresponding bis-allylic ether **9**. OsO_4 -mediated *cis*-dihydroxylation took place from the top face (that is, *anti* to the TBS ether C–O bonds)^[21] in sequential oxidation and protection steps to afford bis-acetonide **10** with complete diastereocontrol. The stereochemistry of this compound was confirmed by a single-crystal X-ray structure determination.^[23] Benzyl and TBS ether deprotection was effected by Birch-type reduction followed by treatment with TBAF to give triol **11**. Selective mesylation and bis-elimination, this time with DBN in toluene, smoothly furnished the diallylic alcohol **12**.



Scheme 4. Synthesis of diallylic alcohol **12**. a) BnBr , NaH , $n\text{Bu}_4\text{NI}$, NMP , 50°C (83%); b) Ph_3PBr_2 , CH_2Cl_2 , RT (87%); c) TBSOTf , 2,6-lutidine, CH_2Cl_2 , RT (98%); d) DBU , 50°C (98%); e) OsO_4 , NMO , $\text{acetone}:\text{H}_2\text{O}$ (5:1), RT (79%);^[22] f) $\text{Me}_2\text{C}(\text{OMe})_2$, TsOH , CH_2Cl_2 , RT (95%); g) $\text{K}_2\text{OsO}_2(\text{OH})_4$, $\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 , MeSO_2NH_2 , quinuclidine, $t\text{BuOH}:\text{H}_2\text{O}$ (1:1), RT (74%); h) $\text{Me}_2\text{C}(\text{OMe})_2$, TsOH , CH_2Cl_2 , RT (98%); i) Na/NH_3 , THF , -78°C , then TBAF , THF , RT (91%); j) MsCl , Et_3N , CH_2Cl_2 , RT (99%); k) DBN , toluene, 110°C (67%). Bn = benzyl, NMP = *N*-methyl-2-pyrrolidinone, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, NMO = 4-methylmorpholine-*N*-oxide, Ts = tosyl = toluene-4-sulfonyl, TBAF = tetrabutylammonium fluoride, DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.

Enantioselective desymmetrization of diallylic alcohol **12** by the Zr-modified Sharpless AE ($\text{Zr}(\text{O}i\text{Pr})_4 \cdot i\text{PrOH}$ (3 equiv), D-(–)-DIPT (3.3 equiv), $t\text{BuOOH}$ (3.4 equiv), CH_2Cl_2 , -20°C , 3 d) afforded epoxy alcohol (+)-**13** in 44% yield (55% accounting for recovered **12**) and >95% *ee*^[24] (Scheme 5).



Scheme 5. Epoxidation of diallylic alcohol **12**.

An analogous reaction with L-(+)-DIPT afforded (–)-**13** in 59% yield (74% accounting for recovered **12**) and >95% *ee*. A control reaction under standard Sharpless AE conditions (that is, stoichiometric $\text{Ti}(\text{O}i\text{Pr})_4/\text{L}-(+)-\text{DIPT}$)^[13] afforded (+)-**13** in 40% yield and just 14% *ee*, which confirms the crucial importance of employing Zr in place of Ti for this type of substrate.

To conclude, we have shown that epoxidative enantioselective desymmetrization of *meso*-decalin diallylic alcohols can be achieved in good yields and with high *ee* values through a Zr-based Sharpless AE process. The utility of the process has been exemplified by its employment for a potentially expedient synthesis of core structures of bioactive *Celastraceae* natural products in which eight contiguous chiral centers are established with >95% *ee* in a single step.

Experimental Section

Procedure for the epoxidative desymmetrization of diallylic alcohol **12**: D-(–)-Diisopropyl tartrate (0.066 mL, 0.31 mmol) was added to a solution of

Zr(OiPr)₄ (109 mg, 0.28 mmol) in CH₂Cl₂ (5 mL) with 4 Å molecular sieves at –20 °C (salt/ice bath), followed by *tert*-butyl hydroperoxide (3.8 M solution in toluene, 0.085 mL, 0.32 mmol). The reaction mixture was stirred at –20 °C for 0.5 h before addition of diallylic alcohol **12** (30 mg, 0.094 mmol) in CH₂Cl₂ (5 mL) which was also cooled to –20 °C. The reaction mixture was then stirred for a further 0.5 h before transfer to a freezer at –20 °C for 3 days. H₂O (2.5 mL) and saturated aqueous Na₂SO₃ (2.5 mL) were added to the reaction mixture. The resulting biphasic system was stirred vigorously for 0.5 h at ambient temperature and the aqueous layer extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried (MgSO₄), filtered through Celite, and concentrated under vacuum. Flash column chromatography (elution with EtOAc:petroleum ether (1:3)) gave epoxy alcohol (+)-**13** as a colorless oil (14 mg, 44 %). (see Supporting Information for analytical data.).

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6/13 and with L-(+)-DIPT gives (–)-**6/13**. This reversal in the sense of induction between the two metals suggests that topologically distinct complexes may be involved. We have yet to establish the absolute configurations of the products but, by analogy with Ti-based AE of other cyclic allylic alcohols, and allowing for the reversal of sense of induction with Zr(OiPr)₄, the configurations drawn in Schemes 3 and 5 would correspond to the levorotatory enantiomers. See: a) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240; b) J. A. Marshall, K. E. Flynn, *J. Am. Chem. Soc.* **1982**, *104*, 7430–7435.

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- [23] Details of this structure determination, full experimental details for all transformations in Schemes 2 and 4, and details of additional studies which led to the selection of this synthetic route will be published in a forthcoming full account of this work.
- [24] *meso*-Bis-epoxide **14** is also formed in 21 % yield. After just 24 h the *ee* value of epoxy alcohol (+)-**13** is 82 % and there are just traces of *meso*-bis-epoxide **14**. Enhancement of the *ee* value as a function of conversion is expected in this type of reaction; see: S. L. Schreiber, T. S. Schreiber, D. B. Smith, *J. Am. Chem. Soc.* **1987**, *109*, 1525–1529.

The First Crystalline Calcium Porphyrin and Tetrakis(*tert*-butylphenyl)porphyrinato Calcium(II): Its Synthesis, Structure, and Binding Properties Towards Alkali and Alkaline Earth Metal Salts**

Lucia Bonomo, Marie-Line Lehaire, Euro Solari, Rosario Scopelliti, and Carlo Floriani*

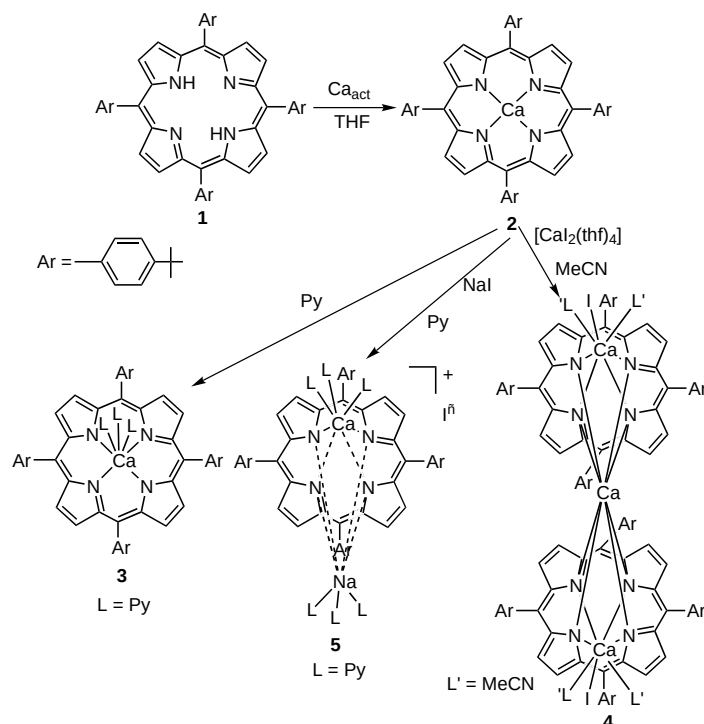
The study of alkaline earth metals and particularly of calcium in porphyrin systems is of great importance because of their relationship to the role of magnesium and iron porphyrin derivatives in naturally occurring systems. This notwithstanding, information available on the synthesis, structure, and spectroscopic properties of calcium porphyrin is practically nonexistent,^[1] with only UV/Vis data being available.^[1a]

The field of alkali metal porphyrin and porphyrin analogues has burgeoned in recent years,^[2] with a significant example being that of calcium porphyrinogen chemistry.^[3] The isolation and characterization of alkaline earth metal porphyrin systems have failed so far because of the use of protic conditions in their synthesis.^[1] Therefore, we turned our

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attention to the synthesis of a calcium porphyrin using nonprotic conditions and a suitably substituted porphyrin, namely 5,10,15,20-tetrakis(4-*tert*-butylphenyl)porphyrin (**1**, $H_2(tBuPP)$;^[4] Scheme 1). The synthesis of **2**^[5] was performed



Scheme 1. Synthesis of the calcium porphyrin **2** and salt complexation.

by treating the free porphyrin **1** in THF with an activated form of calcium metal.^[6] The reaction led to a weakly solvated form of calcium porphyrin **2**,^[7] which dissolves in both THF and benzene to give red-brown solutions. Its structure (1H NMR) was analyzed in MeCN and pyridine. Its UV/Vis spectrum was of the expected normal type, with bands at 430, 572, and 612 nm. The solvated form **3**^[5] was isolated from pyridine and structurally characterized.

The coordinative unsaturation of the calcium ion in **2** was proved by its binding to three pyridine molecules, which have a significant effect on the chemical shift of the β -protons of the pyrrole moieties and the *meso*-aryl protons.^[5] The structure analysis of **3**^[8] shows (Figure 1) there is a significant

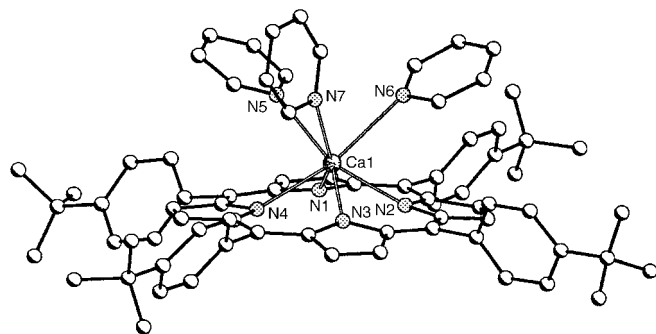


Figure 1. Ball and stick diagram for complex **3** (solvent molecules and hydrogen atoms are omitted). Selected bond lengths [Å]: Ca1–N1 2.382(4), Ca1–N2 2.391(3), Ca1–N3 2.397(3), Ca1–N4 2.416(3), Ca1–N5 2.640(4), Ca1–N6 2.723(4), Ca1–N7 2.663(4).

displacement of the calcium ion from the N_4 plane ($-1.208(2)$ Å). The N(pyrrole)–Ca bond lengths range from 2.382(4) to 2.416(3) Å, with the other structural parameters being in the expected range.

The N_4 core of the porphyrin skeleton in **3** maintains some extra-binding ability towards metal ions. Such a behavior has been emphasized by adding a solution of $[CaI_2(thf)_4]$ ^[9] in acetonitrile to the solution of **2** in acetonitrile (Scheme 1). The 1H NMR spectrum of the resulting solution showed, regardless of the $CaI_2/2$ ratio employed, the appearance of a single new compound (**4**), the amount of which depends exclusively on the reaction time and the temperature. The significant change in the chemical shifts of the β -protons of the pyrrole rings and the pattern of the *meso*-aryl protons, which are well known from the formation of double-decker structures in the tetraarylporphyrin series,^[10] allows the conversion of **2** into **4** to be easily followed. After 24 hours at room temperature, 50 % of **2** was converted into **4**, while a complete conversion was observed when the solution was refluxed overnight (Figure 2). The addition of toluene (C_7H_8) to the acetonitrile solution led to crystals of **4**^[11] ($[(MeCN)_2ICa(tBuPP)Ca(tBuPP)CaI(MeCN)_2] \cdot 4 MeCN \cdot C_7H_8$) which were suitable for X-ray analysis. The 1H NMR spectrum of **4** in acetonitrile is identical to that observed when **2** is mixed with $[CaI_2(thf)_4]$ ^[11] (Figure 2).

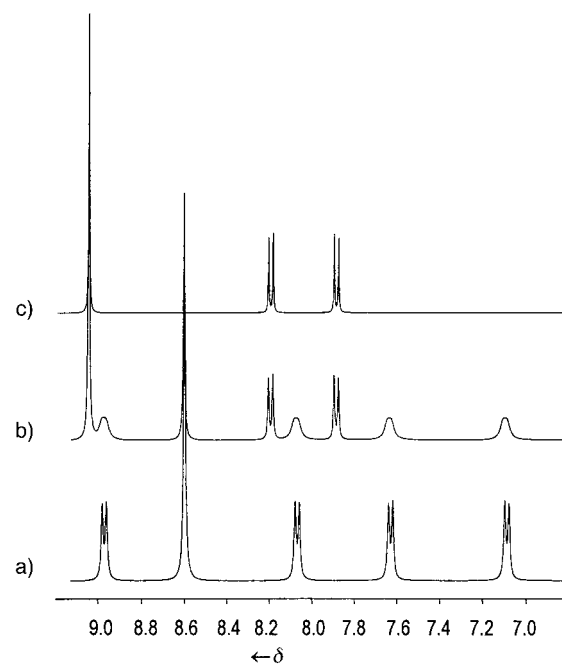


Figure 2. 1H NMR spectra showing the pyrrole and aryl protons of a) **2** in CD_3CN ; b) **2** + $[CaI_2(thf)_4]$ (2:1) after 24 h at room temperature; c) **2** + $[CaI_2(thf)_4]$ (2:1) after 24 h in refluxing CD_3CN .

The structure of **4**^[8] is shown in Figure 3. The molecule can be viewed as a complex of a Ca^{2+} ion sandwiched between two $[Ca(tBuPP)I(MeCN)_2]^-$ ions. The terminal calcium ions protrude from the N_4 plane by 1.577(5) Å, and a coordination geometry quite close to that of the calcium ion in **2** is obtained. In the present case, the Ca–N(pyrrole) bond lengths range from 2.557(10) to 2.589(10) Å. The central calcium ion

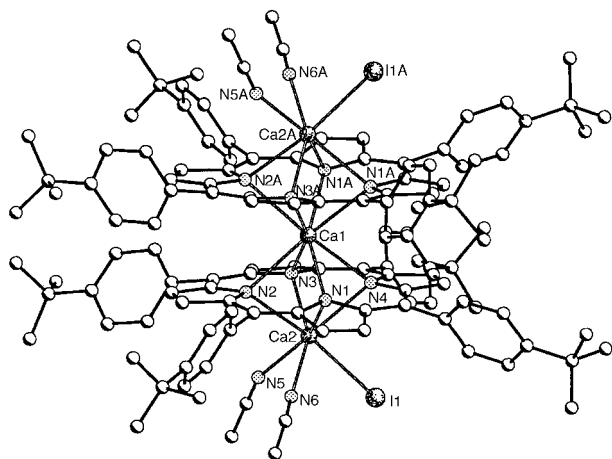


Figure 3. Ball and stick representation of compound **4** (solvent molecules and hydrogen atoms are omitted). Selected bond lengths and distances [Å]: Ca1–N1 2.659(9), Ca1–N2 2.652(9), Ca1–N3 2.557(10), Ca1–N4 2.608(9), Ca2–I1 3.087(3), Ca2–N1 2.589(10), Ca2–N2 2.557(10), Ca2–N3 2.560(9), Ca2–N4 2.571(10), Ca2–N5 2.509(14), Ca2–N6 2.516(12), Ca1...Ca2 3.234(3). The letters A refer to the symmetry transformation $x, -y + 1/2, -z + 1/2$.

is symmetrically bound to the two N_4 cores, with an average Ca–N bond length of 2.619(9) Å and at a distance of $-1.657(5)$ Å out of the N_4 plane. The coordination geometry of the N_8 cage is square antiprismatic. The N_4 core in the alkali metal porphyrin series behaves as a doubly bridging ligand, as shown by analyzing the structures of $[Na_2(OEP)(thf)_4]$ ^[4, 12] and $[K_2(OEP)(thf)_4]$ ^[4, 13]. The coordination of the alkali metal cation by the nitrogen atoms of anionic transition metal porphyrins has been observed in $[Na(THF)_3]_2Fe(TPP)]$ ^[4, 13], $[Na(THF)_3]_2Co(TPP)]$ ^[4, 14] and $[Li_2\{Ru(OEP)Np\}]$ ^[4, 15]. Thallium is also able to sit on another porphyrin moiety, as shown in $[Tl\{Pr(OEP)_2\}]$ ^[4, 16].

The structure is reminiscent of the one of $[AcOHg(Etio)Hg(Etio)HgOAc]$ (Etio = octaalkylporphyrin)^[17] which, however, was only assigned from ^1H NMR data. The binding capability of **2** towards CaI_2 emphasizes for the first time the possibility of metallaporphyrins functioning as salt carriers in moderately polar solvents. The reaction of **2** with NaI confirmed such an assumption with the formation of **5**, whose structure has been supported by an X-ray analysis.^[18] The results presented above prove the stability of the calcium porphyrin derivatives even in quite polar coordinating solvents, except in the protic ones. An interesting perspective is now open for the use of the polar metallaporphyrins as metallaligands for complexing and transporting alkali or alkaline earth metal salts.^[19] This type of complexation can be monitored in CD_3CN by ^1H NMR spectroscopy, since the interaction of the calcium porphyrin with salts causes a significant downfield shift of the protons at the β -position of the pyrrole rings as a function of the specific charge of the cation, while the aryl protons, which give rise to four doublets in **2**, appear as two doublets upon salt complexation, similar to the related metallaporphyrin double-decker structures.^[10]

Experimental Section

2 and **3**: Complex **1** (3.00 g, 3.57 mmol) was added to a suspension of active calcium (3.57 mmol) in THF (250 mL). The reaction mixture was refluxed

for about 24 h. The resulting solution was evaporated to dryness and benzene (250 mL) was added to remove the undissolved NaI. Then the solution was evaporated to dryness to give **2** as a dark violet solid (3.05 g, 97 %). The red crystals of **3** suitable for X-ray diffraction were grown in pyridine. ^1H NMR (400 MHz, CD_3CN , 70 °C, TMS): δ = 8.97 (d, $J(H,H)$ = 7.83 Hz, 4H; CH_{arom}), 8.60 (s, 8H; $CH_{pyrrole}$), 8.07 (d, $J(H,H)$ = 7.83 Hz, 4H; CH_{arom}), 7.63 (d, $J(H,H)$ = 7.83 Hz, 4H; CH_{arom}), 7.03 (d, $J(H,H)$ = 7.83 Hz, 4H; CH_{arom}), 1.69 (s, 36H; tBu); ^1H NMR (400 MHz, C_5D_5N , 80 °C, TMS): δ = 9.04 (s, 8H; $CH_{pyrrole}$), 8.34 (d, $J(H,H)$ = 6.85 Hz, 8H; CH_{arom}), 7.91 (d, $J(H,H)$ = 6.85 Hz, 8H; CH_{arom}), 1.74 (s, 36H; tBu); UV/Vis (CH_3CN): λ_{max} [nm] (ϵ [$mol^{-1}dm^3cm^{-1}$]) = 430 (181582), 572 (9619), 612 (7941); UV/Vis (pyridine): λ_{max} [nm] (ϵ [$mol^{-1}dm^3cm^{-1}$]) = 438 (324960), 574 (11900), 616 (11208); elemental analysis calcd (%) for **2** ($C_{60}H_{60}CaN_4$): C 82.15, H 6.89, N 6.39; found: C 82.01, H 6.79, N 6.42.

4: $[CaI_2(thf)_4]$ (0.163 g, 0.28 mmol) was added to a solution of **2** (0.50 g, 0.57 mmol) in acetonitrile (50 mL). After 24 h of stirring at room temperature, the ^1H NMR spectrum of the reaction mixture recorded at $T = 70^\circ C$ showed the presence of a mixture of **4** and **2** in a 1:2 ratio. After an overnight reflux, the reaction was complete (80 %). The black crystals of **4** suitable for X-ray diffraction were grown from a mixture of acetonitrile and toluene. ^1H NMR (400 MHz, CD_3CN , 70 °C, TMS): δ = 9.04 (s, 8H; $CH_{pyrrole}$), 8.19 (d, $J(H,H)$ = 8.31 Hz, 8H; CH_{arom}), 7.88 (d, $J(H,H)$ = 8.31 Hz, 8H; CH_{arom}), 1.63 (s, 36H; tBu); ^1H NMR (400 MHz, C_5D_5N , 80 °C, TMS): δ = 9.29 (s, 8H; $CH_{pyrrole}$), 8.48 (d, $J(H,H)$ = 6.85 Hz, 8H; CH_{arom}), 7.94 (d, $J(H,H)$ = 6.85 Hz, 8H; CH_{arom}), 1.73 (s, 36H; tBu); UV/Vis (acetonitrile): λ_{max} [nm] (ϵ [$mol^{-1}dm^3cm^{-1}$]) = 422 (195053), 563 (8241), 603 (5491); elemental analysis calcd (%) for **4** ($C_{128}H_{132}Ca_3I_{12}N_{12}$): C 69.50, H 6.01, N 7.60; found: C 69.31, H 6.12, N 7.82.

Salt complexation: An excess of salt (CaI_2 , $CaCl_2$, BaI_2 , NaI) was added directly to the NMR tubes containing solutions of **2** in CD_3CN . The tubes were sealed and heated at 70 °C overnight. ^1H NMR spectrum of **2** in the presence of $CaCl_2$ (400 MHz, CD_3CN , 70 °C, TMS): δ = 9.07 (s, 8H; $CH_{pyrrole}$), 8.17 (d, $J(H,H)$ = 8.0 Hz, 8H; CH_{arom}), 7.90 (d, $J(H,H)$ = 8.0 Hz, 8H; CH_{arom}), 1.65 (s, 36H; tBu); ^1H NMR spectrum of **2** in the presence of BaI_2 (400 MHz, CD_3CN , 70 °C, TMS): δ = 8.97 (s, 8H; $CH_{pyrrole}$), 8.24 (d, $J(H,H)$ = 7.6 Hz, 8H; CH_{arom}), 7.88 (d, $J(H,H)$ = 7.6 Hz, 8H; CH_{arom}), 1.63 (s, 36H; tBu); ^1H NMR spectrum of **2** in the presence of NaI (400 MHz, CD_3CN , 70 °C, TMS): δ = 8.70 (s, 8H; $CH_{pyrrole}$), 8.06 (brs, 8H; CH_{arom}), 7.78 (d, $J(H,H)$ = 8.8 Hz, 8H; CH_{arom}), 1.56 (s, 36H; tBu).

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- For the synthesis and spectroscopic data of **2** and **3**, see the Experimental Section.
- Active calcium prepared according to a known procedure was employed: T. C. Wu, H. Xiong, R. D. Rieke, *J. Org. Chem.* **1990**, 55, 5045.
- Solvation of calcium by aromatic hydrocarbons or acetonitrile seems quite plausible.
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anisotropically refined. For 4420 observed reflections [$I > 2\sigma(I)$] and 804 parameters the conventional R factor is 0.0593 ($wR_2 = 0.1627$ for 9410 independent reflections). Crystal structure analysis of **4**: ($C_{128}H_{132}Ca_3I_2N_{12}$) $\cdot$ $C_7H_8 \cdot 4(C_2H_3N)$, $M_r = 2468.85$, orthorhombic, space group $Pnna$ (No. 52), $a = 16.566(3)$, $b = 34.562(7)$, $c = 24.996(5)$ Å, $V = 14312(5)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.146$ g cm⁻³, $F(000) = 5152$, $\text{MoK}\alpha$ radiation ($\lambda = 0.71070$ Å), $\mu(\text{MoK}\alpha) = 0.598$ mm⁻¹; crystal dimensions $0.13 \times 0.10 \times 0.07$ mm. Data collection and solution of the structure was done as above. For 4480 observed reflections [$I > 2\sigma(I)$] and 742 parameters the conventional R factor is 0.1138 ($wR_2 = 0.3662$ for 9138 independent reflections). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-153000 (**3**) and -153001 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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 [19] Complexation of NaI, CaI₂, CaCl₂, and BaI₂ by **2** has so far been observed.

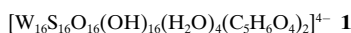
[W₁₆S₁₆O₁₆(OH)₁₆(H₂O)₄(C₅H₆O₄)₂]⁴⁻: A Flexible, Pillared Oxothiotungstate Wheel**

Emmanuel Cadot,* Jérôme Marrot, and
Francis Sécheresse

The design of clusters containing a large number of metal centers represents an intellectually stimulating challenge for the chemist since these compounds are situated at the boundary of molecular and condensed matter. The properties of such compounds are expected to envelop diverse fields such as biochemical processes,^[1] catalysis,^[2] and material science.^[3] In this context, transition metal ringlike clusters based on the {M₂S₂O₂} building block represent a fascinating

emerging class of compounds.^[4] Two years ago, we reported the synthesis and characterization of the neutral ring-shaped polyoxothio molybdenum compound [Mo₁₂S₁₂O₁₂(OH)₁₂(H₂O)₆].^[5] The cyclic architecture of this cluster delimits a central cavity which has a significant cationic character and is the origin of striking properties related to supramolecular^[6] or host–guest chemistry.^[7] Anionic reagents such as phosphate or dicarboxylate ions have been inserted into the cavity replacing the water molecules which initially line the cavity. This substitution led to size-controlled molecular wheels, distorted to a greater or lesser extent, and containing from eight^[8] to twelve^[9] molybdenum atoms. However, compared to heteropolyoxometalates, which are generally built upon Mo, W, and V centers,^[10] cyclic oxothio compounds are restricted exclusively to molybdenum, herein we aim to fill this void.

By acido–basic self-condensation of the {W₂S₂O₂}²⁺ building block we have prepared compound **1** which is the largest



known discrete cyclic oxothioanion. The W₁₆ anion was synthesized through successive steps consisting of the formation of the oxothio precursor [(S_x)₂W₂S₂O₂]²⁻ ($x = 2, 4$)^[11] followed by the selective oxidation of the two terminal polysulfido ligands with stoichiometric amounts of iodine in DMF.^[12] The acido–basic self-condensation was performed in the presence of glutarate which acts as a templating agent. The cesium salt of **1** was isolated as a pale yellow precipitate and after recrystallization at room temperature gave two types of crystals (**1a** and **1b**). A minimum of three weeks was required for the crystallization of orthorhombic crystals of **1a** while the monoclinic phase **1b** crystallized within two or three days.

The compositions of **1a** and **1b** are quite similar, differing only in the water content. The molecular structure of **1** (Figure 1) consists of a cyclic neutral backbone {W₁₆S₁₆O₁₆(OH)₁₆} (noted W₁₆) encapsulating two glutarate ions [C₅H₆O₄]²⁻ (noted glu²⁻). Eight [W₂S₂O₂]²⁺ units are mutually connected by hydroxo double bridges giving two types of W···W separations in the cluster: short W–W distances within the building blocks (2.825(1)–2.818(1) Å for **1a**; 2.813(1)–2.789(1) Å for **1b**) and long inter-block distances (3.413(1)–3.415(1) Å for **1a** and 3.298(1)–3.403(1) Å for **1b**). The two carboxylate groups are symmetrically arranged in the open cavity and exhibit the same type of binding mode with oxygen atoms bonded to the tungsten atoms. The cavity contains four water molecules, each being bonded to a tungsten atom through long W–OH₂ bonds (2.376(9) Å for **1a** and 2.363(10)–2.403(9) Å for **1b**). Probably because of steric constraints induced by the presence of the two glutarate ions in the cavity, four tungsten atoms adopt a pyramidal arrangement. Compounds **1a** and **1b** differ in their packing, the symmetry of the wheel is also significantly affected. In **1a** (orthorhombic), the discrete {W₁₆} cluster has D_{2h} symmetry (Figure 1a) while in **1b** (monoclinic), the symmetry of the wheel is lowered to C_2 (Figure 1b). Both the structures are formally related through “soft” deformations which can be described as antiparallel stretching modes

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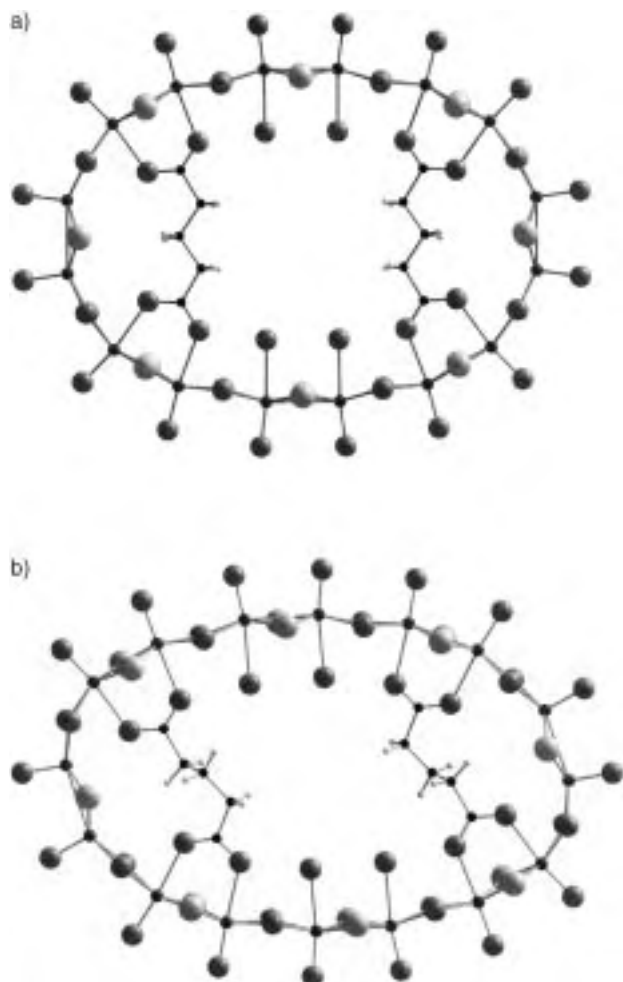


Figure 1. Ball and Stick representations of **1**; a) view of **1a** illustrating the regular $\{W_{16}S_{16}O_{16}(OH)_{16}\}$ elliptic backbone pillared by two glutarate anions; b) view of **1b** showing the distorted elliptic backbone with the two glutaric pillars: (small black sphere: C, small light-gray sphere = H, small dark-gray sphere = W, large light-gray sphere = S, large medium-gray sphere = O).

(Figure 2). Such a result illustrates the high flexibility of a cyclic arrangement, also observed in the analogous Mo_{12} -cyclic oxothiomoledate compound^[7] in which the $\{Mo_{12}\}$ ring can adopt circular or pronounced elliptic geometry provoking strong variations in the Mo-Mo-Mo angles which change from 150° to 130° and 180° .^[5] The two conformations of $\{W_{16}\}$ can be viewed as two snapshots of the molecule, each reflecting the dynamic of the wheel in aqueous solution and the sensitivity of the system to weak interactions.

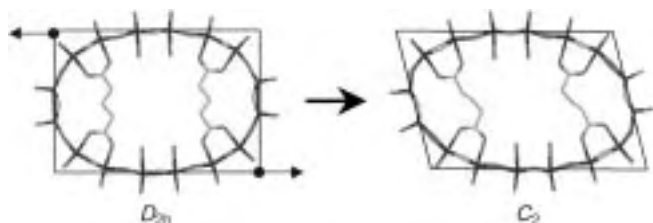


Figure 2. Schematic representation of the D_{2h} – C_2 correlation upon “soft” deformations: arrows symbolize the antiparallel stretching directions.

The ^1H NMR spectra of **1a** or **1b** in D_2O are shown in Figure 3. The encapsulation of the glu^{2-} ion by the $\{W_{16}\}$ ring is characterized by a significant shielding of the ^1H nuclei of

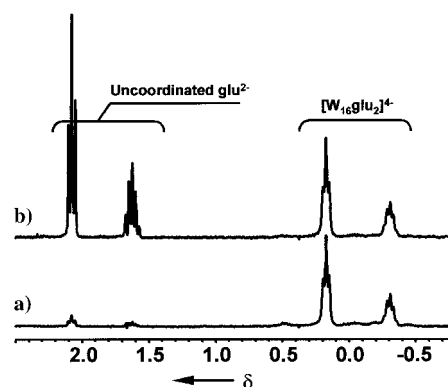


Figure 3. ^1H NMR spectra in D_2O of a) pure $Cs_4[W_{16}glu_2]$ and b) a mixture of $Cs_4[W_{16}glu_2]$ and glu^{2-} .

the methylene unit of the glutarate alkyl chain ($\delta = 0.22$ and -0.26). Resonance signals corresponding to trace amounts of uncoordinated glu^{2-} ions indicate that template exchange can occur, but only in dilute solutions (0.005 M), and only to a small extent (uncoordinated glu^{2-} ions represent less than 2 % of the resonance signals arising from the glu^{2-} ions). The effect of the concentration on the ^1H NMR spectra was studied (Figure 4). As the concentration of the $[W_{16}(glu)_2]^{4-}$

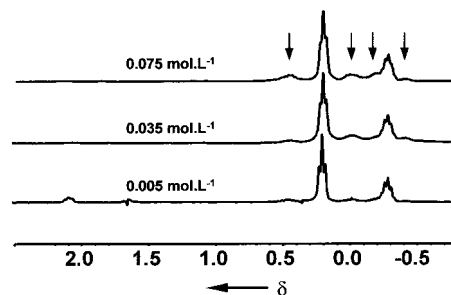


Figure 4. ^1H NMR spectra of $Li_4[W_{16}glu_2]$ in D_2O with variable concentrations in $Li_4[W_{16}glu_2]$. Arrows indicate the resonances attributable to other glu-containing species in equilibrium with $[W_{16}glu_2]^{4-}$.

ion was increased, four broad resonances at $\delta = 0.5$, 0.0 , -0.2 and -0.35 grew; the ^1H NMR spectra show clear features attributable to other glutarate-containing species revealing that equilibria exist involving the $[W_{16}(glu)_2]^{4-}$ ion. Infrared (solid state) and Raman (solution in H_2O) spectra are given in Figure 5. The Raman spectrum is dominated by intense bands corresponding to the $W=O_t$ stretching vibrations (971 cm^{-1} and 955 cm^{-1}) and to the $W-E_{br}$ breathing modes ($E = S$ or O ; 433 cm^{-1} and 418 cm^{-1}). Correlative with Raman features, the infrared spectrum displays in the inorganic region intense absorption bands at 952 cm^{-1} , 530 cm^{-1} , and 425 cm^{-1} , which were tentatively attributed to $W-O_t$, $W-E_{br}$ stretching vibrations, and $W-E_{br}$ breathing modes, respectively. The hydrolytic stability of the complex in solution was studied by UV/Vis spectroscopy. In the pH 4–6 range, the $[W_{16}glu_2]^{4-}$ ion appears stable, but acidification gives back the starting

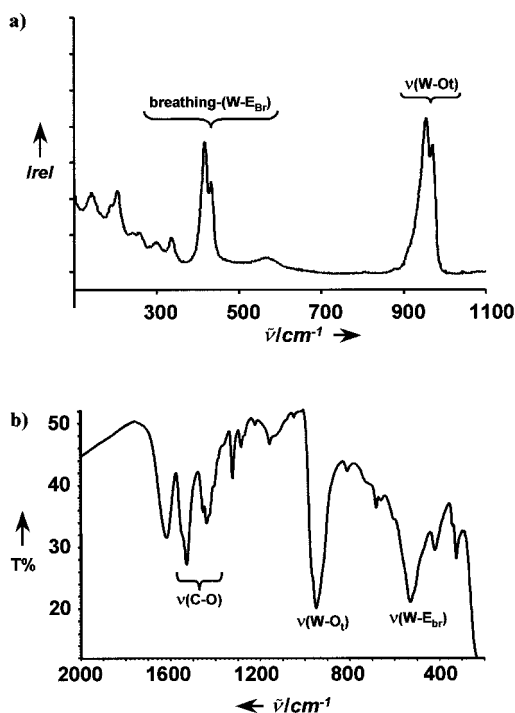


Figure 5. Vibrational spectra of $[W_{16}glu_2]^{4-}$: a) infrared spectrum of $Cs_4[W_{16}glu_2]$ in the solid state and b) Raman spectrum of $Li_4[W_{16}glu_2]$ in aqueous solution, t = terminal, br = bridging.

material $[W_2O_2S_2]^{2+}$ which slowly decomposes with H_2S evolution into insoluble unidentified products.

The results reported herein lead the way to original host–guest chemistry. The use of organic or inorganic templates not only permits the control of the nuclearity of the cyclic cluster (dimension of the wheel) but also the inclusion of specific anionic substrates, a property that is important in transport and extraction processes. Indeed, the possibility to enclose several molecules of substrate in the ring offers some perspectives in the field of homogeneous catalysis, with the inorganic cluster playing the role of a molecular reactor.

Experimental Section

Cs salt of **1:** Iodine (0.585 g; 2.30 mmol) was dissolved in *N,N*-dimethylformamide (5 mL) and slowly added to a stirred solution of $(NMe_4)_2[W_2O_2S_{10}]$ (1 g, 1.15 mmol) in dimethylformamide (10 mL). After the mixture was stirred for 60 min at room temperature, the resulting insoluble material (mainly solid sulfur and tetramethylammonium iodide) was removed by filtration and the red filtrate cooled to 0 °C to complete the precipitation of the remaining NMe_4I . Glutaric acid, $C_5H_8O_4$ (0.15 g; 0.75 mmol) was dissolved in distilled water (15 mL) and the pH of the solution was adjusted to five by addition of NaOH (1.6 mL; 1 mol L⁻¹). The red solution was slowly added to the glutarate solution while the pH was maintained at five by dropwise addition of 1 mol L⁻¹ NaOH (about 2.4 mL of sodium hydroxide was added). The resulting turbid solution was clarified by filtration through a glass frit (D4). The crude product **Cs-1** (yellow solid) was precipitated by addition of cesium chloride (1 g; 6 mmol), collected by filtration, washed with ethanol and dried with diethyl ether (by suction), yield: 0.45 g (50% based on W).

$Cs_4[W_{16}S_{16}O_{16}(OH)_{16}(H_2O)_4(C_5H_8O_4)_2] \cdot 33H_2O$ (1a**):** **Cs-1** (0.2 g) was dissolved in hot water (about 50 °C; 30 mL). After cooling to room temperature, the solution was filtered. The crystallization vessel was covered with a film of paraffin, and the solution allowed to stand for crystallization at room temperature. After three weeks, rectangular parallelepipedic yellow

crystals were isolated; yield: 0.06 g; elemental analysis calcd (%): Cs 9.78, W 54.07, S 9.41, C 2.20; found: Cs 10.08, W 54.03, S 9.45, C 2.12.

$Cs_4[W_{16}S_{16}O_{16}(OH)_{16}(H_2O)_4(C_5H_8O_4)_2] \cdot 34H_2O$ (1b**):** **Cs-1** (0.2 g) was dissolved in hot water (about 50 °C; 20 mL). Then, the solution was filtered and allowed to stand for crystallization in the fume-hood. After three days, yellow diamond-shaped parallelepipedic crystals were isolated; elemental analysis calcd (%): Cs 9.74, W 53.90, S 9.38, C 2.19; found: Cs 10.37, W 54.15, S 9.33, C 2.03.

Synthesis of $Li_4[W_{16}S_{16}O_{16}(OH)_{16}(H_2O)_4(C_5H_8O_4)_2] \cdot nH_2O$. The lithium salt was prepared from crystals of **1a** or **1b** which were dissolved in water and then passed through a cation exchange resin in Li⁺ form (Dowex 50WX2). The resultant solution was evaporated to dryness. The purity of the Li salt was checked by ¹H NMR.

Crystal structure analysis: **1a**: crystal dimensions (0.26 mm × 0.14 mm × 0.10 mm); orthorhombic; space group *Pnmm*; *a* = 11.7504(1), *b* = 20.3808(2), *c* = 24.9664(3) Å, *V* = 5979.02(11) Å³; *Z* = 2; total reflections collected: 32 000; independent reflections: 7998; *R*(int) = 0.0742; a hemisphere of data was collected up to a $2\theta_{max}$ value of 59.30° (92.50% coverage); an empirical absorption correction was applied (SADABS), (μ = 16.883 mm⁻¹; min/max transmission 0.0966/0.2831); structure solution with direct methods and refined by full-matrix least-squares procedure; 263 parameters; *R*₁ = 0.0496 for 5499 independent reflections (*F*_o > 4σ(*F*_o)); highest residual electron density 2.048 Å⁻³. **1b**: crystal dimensions (0.28 mm × 0.16 mm × 0.14 mm); monoclinic; space group *P2₁/n*; *a* = 18.941(3), *b* = 16.272(2), *c* = 20.698(3) Å, β = 107.728(11)°, *V* = 6076.2(14) Å³; *Z* = 2; 40651 reflections; independent reflections: 15 692; A hemisphere of data was collected up to a $2\theta_{max}$ value of 59.45° (90.80% coverage); an empirical absorption correction was applied (SADABS), (μ = 16.614 mm⁻¹; min/max transmission 0.0898/0.2044); structure solution with direct methods and refined by full-matrix least-squares procedure (SHELX-TL package); 475 parameters; *R*₁ = 0.0509 for 7741 independent reflections (*F*_o > 4σ(*F*_o)); highest residual electron density 1.619 Å⁻³. The hydrogen atoms of the alkyl chain of the glutarate were located with geometrical restraints in the riding mode. The two crystals **1a** and **1b** were mounted in Lindemann tubes to prevent any water loss. Crystal data were collected at room temperature (293 K) with a Siemens SMART three-circle diffractometer equipped with a CCD bidimensionnal detector using MoK α monochromated radiation (λ = 0.71073 Å). An empirical absorption correction was applied (SADABS program) based on Blessing's method^[13] and the structures were solved and refined with the SHELX-TL package.^[14] The structural graphics were generated with the program DIAMOND 2.1 K (K. Brandenburg, Crystal Impact GbR, 1999). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-146999 (**1a**) and -147000 (**1b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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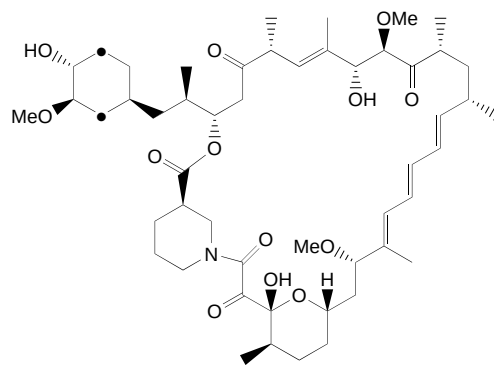
Origin and True Nature of the Starter Unit for the Rapamycin Polyketide Synthase**

Philip A. S. Lowden, Barrie Wilkinson,
Günter A. Böhm, Sandeep Handa, Heinz G. Floss,
Peter F. Leadlay, and James Staunton*

Rapamycin is a polyketide macrolide produced by *Streptomyces hygroscopicus* that displays potent immunosuppressant activity.^[1] The recognition that such a property could be therapeutically useful has generated great interest in the chemistry^[2] and biology^[3] of rapamycin, and of the structurally similar immunosuppressants FK 506 and FK 520.

Rapid progress has been made in the manipulation of polyketide biosynthesis,^[4] and the entire biosynthetic gene cluster for rapamycin has been sequenced.^[5] The rapamycin polyketide synthase (PKS) is a modular system in which 14 chain extension modules are housed in three giant multimodular proteins (RAPS1–3).^[4, 5] The polyketide origin of rapamycin has been verified through feeding studies with labeled precursors.^[6] Rapamycin, FK 506, and FK 520 share in common an unusual substituted cyclohexane ring, the origins of which have been traced to shikimic acid for rapamycin^[7] and FK 520,^[8] and which undergoes O-methylation post-PKS

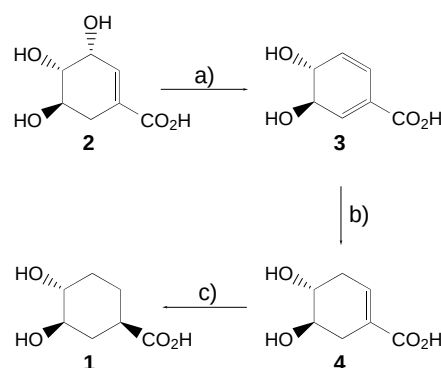
during the biosynthesis of FK 506.^[9] The proximal precursor for this unusual starter unit for rapamycin biosynthesis has been shown to be (1*R*,3*R*,4*R*)-3,4-dihydroxycyclohexanecarboxylic acid (**1**, DHCHC).^[10] That the saturated molecule **1** is



Rapamycin

the starter unit of the rapamycin PKS brings into question the function of an apparently catalytically competent enoyl reductase domain (ER) present in the initiation module,^[5] the structure of which is also conserved for the PKSs of FK 506^[11] and FK 520.^[12]

The steps between shikimic acid (**2**) and **1** for FK 520 have been elucidated and are described in Scheme 1.^[8, 13] An initial *anti*-1,4-conjugate elimination of water from **2** provides



Scheme 1. Biosynthetic pathway to DHCHC (**1**) in FK 520 and rapamycin. a) Stereospecific 1,4-*anti*-elimination of water; b) reduction of the Δ^1 double bond and isomerization of the remaining double bond from Δ^2 to Δ^1 ; c) reduction of the final Δ^1 double bond.

(4*R*,5*R*)-4,5-dihydroxycyclohexa-1,5-dienecarboxylic acid (**3**). The α,β -double bond is then reduced in a *syn* fashion and the system subsequently undergoes a suprafacial 1,3-allylic rearrangement to form 4,5-dihydroxycyclohex-1-enecarboxylic acid (**4**). A final *anti* reduction of the conjugated double bond provides **1**. This pathway is related to that which was elucidated for the cyclohexanecarboxylic acid (CHC) precursor of ω -cyclohexyl fatty acids in *Alicyclobacillus acidocaldarius*^[14] and of ansatrienin A in *Streptomyces collinus*.^[15] Herein we will attempt to address the question of the identity of the intermediates between shikimic acid and **1** during rapamycin biosynthesis.

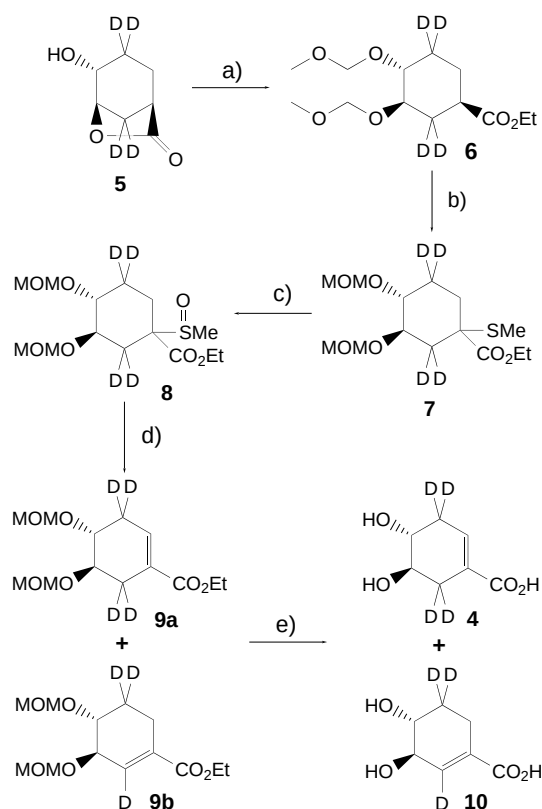
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Stereospecifically deuterated (–)-(6*R*)-[6-²H₁]- and (–)-(6*S*)-[6-²H₁]-shikimic acids^[16] (see **2**) were fed separately (to provide a final concentration of 1 mM) to growing cultures of *S. hygroscopicus* (ATCC 29253) after 24 h. After a total of four days growth the mycelia were harvested, extracted with methanol, and the rapamycin was purified by reversed-phase HPLC. Analysis by ²H NMR spectroscopy, liquid chromatography–electrospray mass spectrometry, and high-resolution mass spectrometry confirmed that the pro-6_R proton is stereospecifically lost during the biosynthesis of rapamycin; the specific incorporation of **2** was measured at 25%. Thus, the conversion of **2** into **3** proceeds through an *anti*-1,4-conjugate elimination of water with loss of the pro-6_R proton, as do the analogous reactions during FK 520^[13] and CHC biosynthesis.^[16] In a similar manner, incorporation of the cross-conjugated diene **3**^[15] was confirmed (79% specific incorporation). These data clearly indicate the intermediacy of these two species during rapamycin biosynthesis, which most probably mirrors the process leading to FK 520. The specific incorporation levels that we observed are striking. In isolation, the very high specific incorporation of saturated **1** reported previously (44%) strongly implicated this molecule as the specific starter unit for the rapamycin PKS; as a control we repeated the feeding of **1** in parallel to those above and obtained a value of 52%. However, the striking data for **2** and **3** prompted us to question the true intermediacy of **1**, and further to investigate whether **4**, the unsaturated biosynthetic precursor of **1**,^[8] could be the true starter unit for the rapamycin PKS.

To examine this question we developed a stereocontrolled route to **4** (Scheme 2) that utilized an intermediate from our chiral synthesis of [²H₄]-**1**.^[10] Thus, the hydroxylactone **5** was readily converted into the bis-MOM-protected ethyl ester **6** in two steps. This material was then added to LDA and the lithium enolate thus formed quenched with dimethyl sulfide. The resultant thioether **7** was partially purified before treating with sodium periodate to provide sulfoxide **8**. This compound was then heated in refluxing toluene to provide a 2:1 mixture of the regioisomers **9a** and **9b**. This route takes advantage of a primary isotope effect to direct elimination in favor of the desired compound **9a** (2:1 versus 1:1.3 using non-deuterated **8**). The mixture of **9a** and **9b** was not separable but, provided **4** and **10** after deprotection. It was possible to use this mixture to test the intermediacy of **4** as a result of the differing deuterium content of the two molecules. On feeding this material to *S. hygroscopicus* we were gratified to observe selective incorporation of the [²H₄]-**4** species with a remarkable 87% specific incorporation. This immediately indicated that **4** may indeed be the true starter unit for the rapamycin PKS. To verify the intermediacy of **4**, and by implication show that **1** is incorporated adventitiously into rapamycin as a result of some broad substrate tolerance in the PKS initiation module, we performed a series of competition feeding experiments utilizing the labeled [²H₄]-**1** and -**4** in conjunction with their unlabeled, racemic equivalents, which were prepared following literature procedures.^[15] Each precursor was fed as the enantiomerically enriched, labeled form (1 mM) along with varying concentrations of the other precursor in its racemic, unlabeled form (Table 1). The data



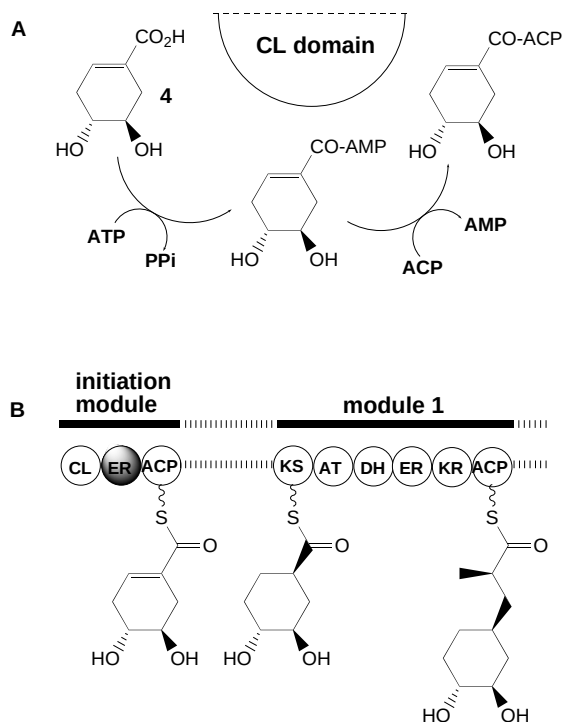
Scheme 2. Synthesis of the labeled precursor **4**. a) 1. KOH, EtOH, 2. CH₃OCH₂Cl, *i*Pr₂NEt (99%); b) 1. LDA, 2. MeSSMe; c) NaIO₄, MeOH (70%); d) Δ/toluene (67%); e) 1. HCl, MeOH, 2. KOH, H₂O (90%). LDA = lithium diisopropylamide, MOM = methoxymethyl.

Table 1. Results of competition feeding experiments between compounds **1** and **4**. The *m/z* 936.5 peak corresponds to the sodium ion adduct of rapamycin, and *m/z* 940.5 to the equivalent ²H₄-labeled isomer. The concentration of the unlabeled precursor refers to that for the enantiomer that corresponds to rapamycin.

² H ₄ -labeled precursor [mM]	Unlabeled precursor [mM]	Intensity of <i>m/z</i> 936.5 peak [%]	Intensity of <i>m/z</i> 940.5 peak [%]
1 (1)	4 (0.05)	50	50
1 (1)	4 (0.25)	81	19
1 (1)	4 (0.5)	89	11
4 (1)	1 (0.5)	2	98
4 (1)	1 (1)	9	91
4 (1)	1 (5)	23	77

obtained clearly indicated that **4** is indeed the preferred starter unit, even when fed in the presence of a fivefold excess of **1**. Conversely, the ability of **1** to act as the starter unit was significantly inhibited in the presence of unlabeled **4**, even when present at a concentration of only 0.25 mM. It is further noteworthy that the absolute levels of rapamycin were not significantly affected by the feeding conditions, which indicates that the remarkably high levels of specific incorporation were not an experimental artefact. Furthermore, these high specific incorporations indicate no limitation in the substrate penetrating the cell membrane and progressing to the site of biosynthesis. These data also lend support to the notion that the precursors of **4** are formed *de novo* in the free acid form before activation immediately prior to the loading of the PKS.

The data in this report, in conjunction with the N-terminal structure of the rapamycin PKS, allow us to identify **4** as the true starter unit for the rapamycin PKS. The differing stereospecificity of the enoyl reductions during the biosynthesis of **1** for FK520, and by extrapolation for rapamycin, is consistent with the use of the initiation module ER domain.^[17] The differences in stereochemical detail between the biosynthesis of **1**,^[8] and the biosynthesis of CHC^[14, 15] suggest that precursors of **4** occur as the free acids.^[18] By analogy to non-ribosomal peptide synthesis^[19] we suggest (Scheme 3) that the



Scheme 3. A) Proposed pathway for CL-catalyzed activation and subsequent attachment of **4** to the rapamycin PKS; B) translocation of ACP-bound **4** involves reduction of the Δ^1 bond by the initiation module ER domain prior to chain elongation on module one of RAPS1, the N-terminus of which is shown with a linear arrangement of the predicted catalytically active domains. AMP = adenosine monophosphate; P_i = inorganic phosphate; CL = carboxylic acid ligase; ER = enoyl reductase; ACP = acyl carrier protein; KS = β -ketoacyl synthase; AT = acyl transferase; DH = dehydratase; KR = β -ketoacyl reductase.

CL domain catalyses formation of an AMP-activated form of **4**, which is subsequently transferred to the ACP domain. Reduction by the ER domain is followed by transfer to the KS1 domain of RAPS1 to initiate chain elongation. The observation that **1** can also be directly incorporated points to a broad substrate specificity in the CL domain which may allow for its use for the production of analogues of rapamycin by incorporation of a variety of alicyclic starter acids.

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A Novel Approach for the One-Pot Preparation of α -Amino Amides by Pd-Catalyzed Double Carbohydroamination**

Yong-Shou Lin and Howard Alper*

Developing new synthetic methods for the preparation of amino acids and their derivatives has attracted much attention due to their applications to the fine chemical, agrochemical, and pharmaceutical business sectors.^[1] Although a variety of elegant routes has been discovered for the synthesis of amino acids, amidocarbonylation (Wakamatsu reaction) is the only method involving a transition metal complex catalyzed three-component reaction of an aldehyde, an amide, and carbon monoxide.^[2] Domino reactions, which include amidocarbony-

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lation, have proven effective for the one-pot synthesis of organic compounds.^[3]

The first double carbonylation reaction, for introducing two adjacent CO groups into an organic moiety, was found by using cobalt carbonyl complexes as catalysts in converting benzyl halides to the corresponding arylpyruvic acids.^[4] Development of the double carbonylation reaction has been realized, for example, in the conversion of aryl and alkenyl halides to the corresponding α -ketoamides and esters by using palladium complexes as catalysts,^[5] and in the synthesis of α -ketolactones from epoxides by phase-transfer Co-catalyzed reactions.^[6] It is also known that α -keto acids are precursors of α -amino acids.^[7] Research in our laboratory has previously led to useful methods for the hydrogenation of imines, α -ketoesters, and α -ketoamides.^[8] We now report a new domino reaction, involving a sequence of double carbonylation, amine condensation, and hydrogenation to produce α -amino amides.

Initial experiments were conducted by using iodobenzene, cyclohexylamine (**1a**), carbon monoxide (800 psi; 1 psi = 6894.76 Pa), hydrogen (100 psi), and Pd on charcoal as the

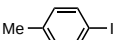
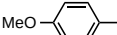
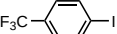
amino acid derivatives, a previous case being Co- and Pd-catalyzed amidocarbonylation.^[2] α -Amino amides, like α -amino acids and their derivatives, are of medicinal value.^[9]

The structure of the cyclohexylamino amide **2a** was established by ¹H and ¹³C NMR spectroscopy, mass spectrometry, as well as by elemental analysis.^[10] In addition to the formation of **2a**, cyclohexylamide (**3a**) was obtained as a by-product, and traces to small amounts of α -N-cyclohexylimino amide (**4a**) and N-benzylidenecyclohexylamine were also detected in the reaction mixture. Various reaction conditions were examined and the results are listed in Table 1. Addition of triethylamine is essential for obtaining a higher proportion of **2a** over **3a** (Table 1, entry 2). In the absence of 4 Å molecular sieves, some **4a** was formed thus reducing the yield of the amino amide (Table 1, entry 3). Reducing the reaction temperature from 120 °C to 105 °C lowered the conversion of iodobenzene to **2a** (Table 1, entry 4). Increasing the hydrogen pressure from 100 to 400 psi afforded 5 % of PhCH₂NHCy (by hydrogenation of the other by-product PhCH=NCy, Table 1, entry 6). In all of the reactions, an ammonium iodide RNH₃⁺I⁻ was formed as a salt.^[11]

Primary amines other than cyclohexylamine can also be used for the reaction. *n*-Butylamine (**1b**) gave the corresponding α -amino amide (**2b**) in 67 % yield together with 29 % of amide **3b** (Table 1, entry 7).^[10] Using benzylamine (**1c**) gave **2c** in only 24 % yield, **3c** in 34 % yield, and several other by-products (Table 1, entry 8).

The double carbonylation reaction is applicable to various iodoarenes, giving the corresponding α -amino amides **5** usually as the dominant products, together with amide **6** (Table 2).^[10] Iodoarenes with electron-donating or electron-withdrawing substituents afforded α -amino amides in 60 to 88 % yields (Table 2, entries 1–5). Except for *p*-iodotrifluoromethylbenzene, the amides were formed in low yields.

Table 2. Pd-catalyzed double carbonylation of aromatic iodides.^[a]

Arl + CyNH ₂		Pd/C, CO/H ₂ NEt ₃ , 4 Å, 120 °C - CyNH ₃ ⁺ I ⁻		Ar-CH(NH-Cy)-C(=O)-NH-Cy		Ar-C(=O)-NH-Cy	
				5		6	
Entry	ArI	5	Yield [%] ^[b]	6	Yield [%] ^[b]		
1 ^[c]		5a	88	6a	6		
2 ^[c,d]		5b	68	6b	13		
3 ^[c,d]		5c	65	6c	17		
4		5d	60	6d	40		
5 ^[c,d]		5e	64	6e	18		

[a] Reaction conditions: Iodide (1 mmol), cyclohexylamine (10 mmol), NEt₃ (3 mL), 4 Å molecular sieves (1 g), 10 % of Pd/C (0.02 mmol), CO (800 psi), and H₂ (100 psi) were employed at 120 °C for 24 h. [b] Yields were determined based on ¹H NMR spectroscopy. [c] Trace amounts of ArCH=NCy were detected. [d] A small amount of α -imino amide (less than 3 %) was detected in the mixture.

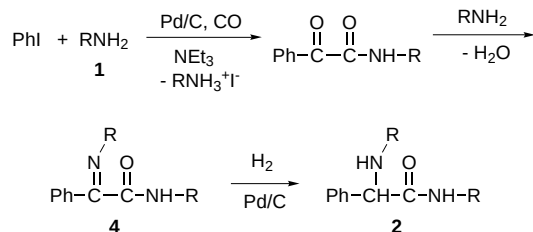
catalyst in the presence of triethylamine and 4 Å molecular sieves [Eq. (1); **a**: R = cyclohexyl, **b**: R = *n*-butyl, **c**: R = benzyl]. This reaction proceeded well to form α -cyclohexylamino amide (**2a**, R = cyclohexyl) as the major product (87 % yield, Table 1, entry 1). To our knowledge, this novel domino reaction, *double carbonylation*, is unprecedented and the first example of a one-pot preparation of α -amino amides from the corresponding aryl halides. In addition, it is a rare example of the transition metal catalyzed formation of α -

Table 1. Palladium-catalyzed double carbonylation of iodobenzene.^[a]

Entry	Amine	CO [psi]	H ₂ [psi]	T [°C]	Products [%] ^[b]		
					2	3	4
1 ^[c]	1a	800	100	120	87	5	0
2 ^[d]	1a	800	100	120	59	41	trace
3 ^[c,e]	1a	800	100	120	66	18	10
4	1a	800	200	105	46	18	18
5 ^[c]	1a	700	300	120	77	9	trace
6 ^[f]	1a	800	400	120	73	8	0
7	1b	700	300	120	67	29	trace
8 ^[g]	1c	800	100	120	24	34	5

[a] Reaction conditions: PhI (1 mmol), amine (10 mmol), Et₃N (3 mL), 4 Å MS (1 g), 10 % of Pd/C (0.02 mmol), and CO/H₂ were employed in the reactions for 24 h. [b] The yields were determined by ¹H NMR spectroscopy. [c] A small amount of PhCH=NCy (less than 5 %) was obtained. [d] The reaction was carried out by using **1a** (4 mL) as solvent instead of Et₃N. [e] The reaction was carried out in the absence of 4 Å molecular sieves. [f] PhCH=NCy (5 %) and PhCH₂NHCy (5 %) were also formed as by-products. [g] PhCH=NHCH₂Ph (31 %) and a small amount of (PhCH₂)₂NH were produced.

A possible pathway for the formation of α -amino amides (Scheme 1) may involve the following sequence: double carbonylation of the iodoarene to give the α -keto amide,



Scheme 1. Reaction pathway for the double carbonylation of iodobenzene. **a**: R = cyclohexyl, **b**: R = *n*-butyl, **c**: R = benzyl.

amine condensation with the α -keto group of the latter to form an α -imino amide **4** as an intermediate, and hydrogenation of the imino double bond of **4** to give the α -amino amide **2**. α -Keto amide formation in the double carbonylation process can be considered to be related to that described by Yamamoto and co-workers, via formation of an acylcarbamoylpalladium intermediate followed by reductive elimination.^[12] Palladium-catalyzed double carbonylation of aryl halides in the presence of a secondary amine to give α -keto amides has been extensively studied.^[13] Using a primary instead of a secondary amine in the double carbonylation reaction has only been described in several papers.^[5b, 12] However, the double carbonylation reaction sequence, described herein can, for the first time, produce α -amino amides in a one-pot manner. The formation of the amide by-product results by monocarbonylation of iodobenzene. The formation of the by-product imine can be attributed to competitive reactions of hydroformylation of iodobenzene with subsequent amine condensation.

In conclusion, palladium-catalyzed double carbonylation, consisting of double carbonylation, amine condensation, and hydrogenation, is a novel domino reaction for the one-pot production of α -amino amides. The reaction is simple in execution and workup, and is of considerable potential for the synthesis of α -amino amides and other α -amino acid derivatives.

Experimental Section

General procedure for the double carbonylation: A mixture of iodobenzene (0.112 mL, 1 mmol), cyclohexylamine (1.14 mL, 10 mmol), triethylamine (3 mL), Pd/C (10%, 0.0213 g, 0.02 mmol), and 4 Å molecular sieves (1 g) was placed in a 45-mL stainless steel autoclave equipped with a glass liner and magnetic stirrer. The autoclave was purged three times with carbon monoxide and then pressurized with CO and H₂, respectively, to the desired level (see Tables 1 and 2). The reaction was carried out in an oil bath for 24 h and the autoclave was cooled to room temperature and the gas was released. The reaction mixture was filtered through Celite, washed several times with CH₂Cl₂, and filtrate was evaporated to give a pale yellow oily residue. Addition of ether gave a white precipitate, identified as CyNH₃⁺I⁻. After filtration, the diethyl ether solution was evaporated and the resulting oil was subjected to ¹H NMR spectroscopy, and then to preparative TLC, using hexane/ethyl acetate as eluant, affording the pure α -amino amide.^[10]

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A Neutral Three-Coordinate Alkylrhodium(0) Complex: Stabilization of a 14-Electron Species by γ -C–H Agostic Interactions with a Saturated Hydrocarbon Group**

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Selective activation and functionalization of alkanes by transition metals is a highly attractive goal^[1] which has led to considerable efforts to understand hydrocarbon interactions

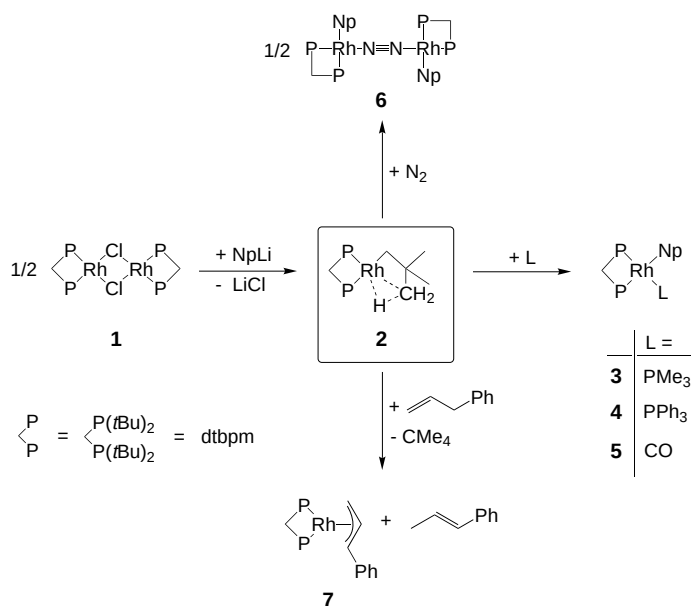
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with vacant sites of transition metal centers. Three-coordinate, T-shaped, 14-electron d^8 -ML₃ complexes play a vital role as key intermediates in many stoichiometric and catalytic transformations,^[2] as exemplified by [RhCl(PPh₃)₂] from Wilkinson's catalyst and its congeners.^[2a,3] Usually they are transient species generated in situ by ligand dissociation^[4] or by hapticity changes of, for example, η^3 -benzylic systems [L₂M(η^3 -CH₂Ph)] (M = Rh, Ir).^[2b,5] Stabilization of 14-electron d^8 -ML₃ species has been achieved by using bulky *trans* ligands in *trans*-[RhX(PR₃)₂] complexes (X = H, Hal, σ -carboranyl; R = *t*Bu, *i*Pr, Cy, Ph), but their monomeric nature is either only postulated or deduced from molecular weight measurements in solution.^[6,7] To date, only [Rh(PPh₃)₃]⁺, [Ni(Mes)₃][−] (Mes = 2,4,6-(CH₃)₃C₆H₂), and the olefin complexes [(LN₂)Rh(η^2 -ene)] (LN₂ = β -diimine; ene = cyclooctene, norbornene) have been structurally characterized.^[8]

Here we report the synthesis, structure, and reactivity of the first neutral, three-coordinate alkylrhodium(I) complex [(κ^2 -dtbpm)RhNp] (**2**), which contains the *cis*-chelating bis(di-*tert*-butylphosphanyl)methane^[9] ligand (*t*Bu₂PCH₂Pr*t*Bu₂, dtbpm) and a neopentyl (Np) group (Scheme 1). The 14-electron Rh^I



Scheme 1. Synthesis and some reactions of **2**.

center is weakly stabilized by agostic interactions with the γ -C–H bonds and possibly the β -C–C bond of the alkyl ligand. Owing to the availability of an “open” coordination site, **2** is an ideal model of uncharged three-coordinate d^8 -[L₂Rh(alkyl)] transients and of isoelectronic, d^8 -[L₂M(alkyl)]⁺ ions (M = Ni^{II}, Pd^{II}), intermediates in late transition metal catalyzed olefin polymerization.^[10]

Treatment of [(κ^2 -dtbpm)RhCl]₂ (**1**)^[6] with an excess of NpLi in a pentane suspension at −20 °C led to air- and moisture-sensitive **2** in 61% yield.^[11] The orange-red compound is moderately stable at 25 °C as a solid, but solutions of **2** have to be handled at lower temperatures, as rapid, unselective decomposition is observed above 0 °C. A single-crystal X-ray diffraction analysis of **2** revealed the expected planar T-shaped RhP₂C skeleton (Figure 1).^[12]

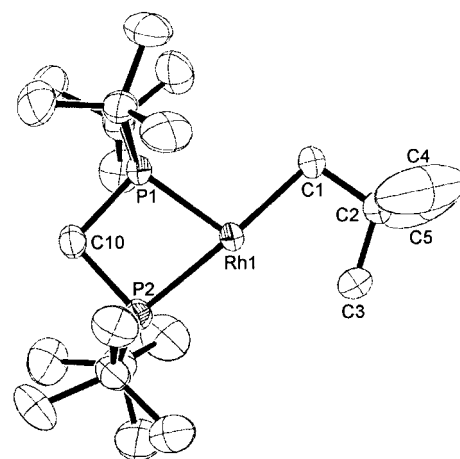


Figure 1. Molecular structure of **2** (ORTEF plot, 50% probability ellipsoids, hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: Rh1–P1 2.172(1), Rh1–P2 2.314(1), Rh1–C1 2.082(4), Rh1–C2 2.804, Rh1–C3 2.491(4), C1–C2 1.521(5), C2–C3 1.498(5), C2–C4 1.443(6), C2–C5 1.463(6); P1–Rh1–P2 75.98(4), C1–Rh1–P1 101.01(11), C1–Rh1–P2 176.60(14), Rh1–C1–C2 101.0(2), C1–C2–C3 109.0(3). Estimated Rh–H3 (assuming standard C–H bond lengths and angles): 1.55 (one H at C3 agostic) or 2.23 (for wedge position of two agostic hydrogen atoms).

The unsymmetric chelate ring Rh1–P1–C10–P2 and atoms C1, C2, and C3 of the neopentyl group are almost coplanar. The long Rh1–P2 bond (2.314(1) Å) is a consequence of the strong *trans* influence of the alkyl ligand, which is also reflected in the small Rh–P2 coupling constant^[13] ¹J(P,Rh) of 99 Hz for P2 (dd, δ = 21.6). The short Rh1–P1 bond of 2.172(1) Å and the correspondingly large ¹J(P,Rh) coupling constant of 280 Hz for the resonance of P1 (dd, δ = 54.2) indicate a nearly negligible *trans* influence of the agostic hydrocarbon moiety.

The nature of this agostic interaction in **2** was studied by low-temperature ¹H NMR spectroscopy in [D₈]THF and [D₈]toluene.^[11] All three methyl groups of the neopentyl ligand remain equivalent on the ¹H NMR time scale down to −105 °C, implying a very small rotational barrier for the neopentyl *t*Bu group. The methyl doublet resonance (²J(H,P) = 2.2 Hz, assigned by ¹H and ¹H{³¹P} NMR spectra) at δ = 0.83 (−30 °C, [D₈]THF) confirms time-averaged γ -agostic interactions of all nine C–H bonds with the rhodium center.^[14] It is impossible to establish the weak γ -C–H to Rh σ -complexation through C–H bond elongation in the solid-state structure, because the neopentyl methyl hydrogen atoms could not be localized. The very short^[15] nonbonded Rh1–C3 distance of 2.491(4) Å and the small Rh1–C1–C2 angle (101.0(2)°), however, clearly reveal an attractive relationship of the metal center with one or two γ -C–H bonds and possibly with the C2–C3 bond in the β -position. In fact, this bond undergoes clean β -methyl elimination in the isoelectronic platinum cation [(κ^2 -dtbpm)PtNp]⁺, leading to isobutene and a metal-bound methyl group.^[16] Thus, rhodium compound **2** might resemble a structure on the pathway of β -carbon elimination at d^8 -ML₂ templates.^[17]

Owing to the averaging out of all nine methyl protons of the Np group by *t*Bu and Me rotations, lowered C–H stretching frequencies, upfield NMR shifts, or reduced ¹³C–¹H coupling constants for the agostic hydrogen atoms are not observed for

2.^[15] However, agostic interactions are unequivocally established for the solid-state structure and by all NMR data of **2** in solution.

The inequivalence of the two P nuclei at ambient temperature proves that barrier for T-Y-T inversion at the rhodium center lies well above 20 kcal mol⁻¹, consistent with theoretical predictions.^[6,18]

Agostic interactions in **2** were probed by density functional theory (DFT) calculations^[19] on the model system [(κ^2 -dhpm)RhNp] (**2a**; dhpm = bis(diphosphanyl)methane, H₂PCH₂PH₂). Its optimized geometry (Figure 2) is in good agreement with the solid-state structure of **2** and clearly displays an agostic C–H bond to the vacant coordination site.

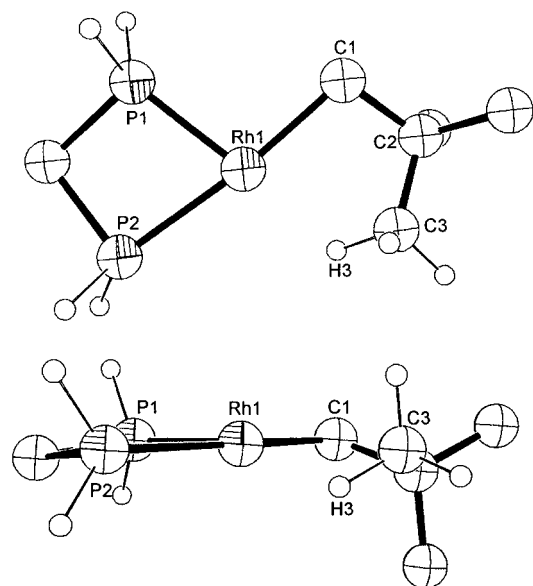


Figure 2. Optimized geometry of the model complex **2a** (DFT; some hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: Rh1–P1 2.190, Rh1–P2 2.360, Rh1–C1 2.057, Rh1–C2 2.795, Rh1–C3 2.521, Rh1–H3 1.997, C1–C2 1.541, C2–C3 1.546, C3–H3 1.128; P1–Rh1–P2 74.2, C1–Rh1–P1 99.2, C1–Rh1–P2 173.4, Rh1–C1–C2 101.0, C1–C2–C3 105.2.

The metal-coordinated C3–H3 bond is elongated (1.128 Å compared to an average of 1.097 Å for the noncoordinated C–H bonds), and the short Rh–H3 distance (1.997 Å) indicates a moderately strong interaction, which is also reflected in the computed low C3–H3 vibrational frequency of 2723 cm⁻¹ and the short (2.190 Å) Rh–P1 distance (as opposed to Rh–P2, 2.360 Å), which establishes the weak donor character of the agostic C–H bond. The NMR equivalence of the nine methyl protons of **2** corresponds to tiny calculated barriers to rotation for the methyl (0.5 kcal mol⁻¹) and *t*Bu groups (2 kcal mol⁻¹) for **2a**. Neopentyl rotation occurs through a three-coordinate T-shaped transition state (8.6 kcal mol⁻¹) without σ complexation of C–H bonds.

In NMR experiments, ligands L (L = PMe₃, PPh₃, CO) instantaneously react with **2**, yielding square-planar complexes [(κ^2 -dtbpm)RhNpL] **3–5** (Scheme 1). Compounds **3** and **5** were synthesized independently from NpLi, [(κ^2 -dtbpm)RhCl(PMe₃)],^[6] and [(κ^2 -dtbpm)RhCl(CO)].^[6] Their

structures were established by X-ray diffraction.^[12b,c] Unlike **3** and **5**, **4** dissociates in solution, forming **2** and PPh₃.

Treatment of a solution of **2** in pentane with 1 bar of N₂ led to the precipitation of the air- and moisture-sensitive dinuclear, dinitrogen-bridged complex [(κ^2 -dtbpm)RhNp]₂(μ - η^1 : η^1 -N₂) (**6**) (Figure 3).^[12b] To our knowledge, **6** represents the first dinuclear, doubly end-on dinitrogen-bridged, late transition metal complex with a *cis*-chelating diphosphane ligand.^[20] Orange, sparingly soluble **6** is stable as a solid at ambient temperature, but loses N₂ in vacuo, undergoing undefined decomposition. In solution, N₂ loss above –10 °C regenerates **2**.

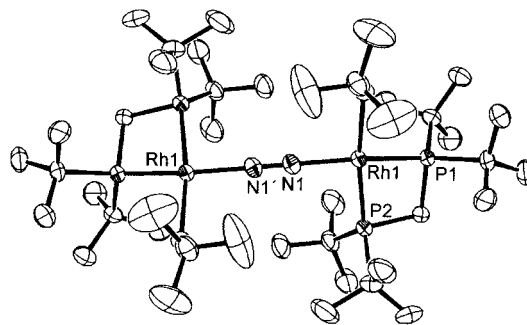


Figure 3. Molecular structure of **6** (ORTEP plot, 50% probability ellipsoids, hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: Rh1–P1 2.258(1), Rh1–P2 2.322(1), Rh1–C1 2.133(4), Rh1–N1 1.973(3), N1–N1' 1.106(6); P1–Rh1–P2 75.35(4), N1–Rh1–C1 92.36(15), N1–Rh1–P1 166.42(9), N1–Rh–P2 95.99(10), N1'–N1–Rh1 169.56(9).

The alkylrhodium complex **2** also coordinates olefins and activates C–H bonds under mild conditions. The NMR spectrum recorded for the reaction of a solution of **2** in [D₈]THF with an excess of allylbenzene at –70 °C indicates the formation of two transient species. On raising the temperature, these transient species undergo benzylic C–H activation and neopentane elimination. The stable allylic complex [(κ^2 -dtbpm)Rh(η^3 -1-Ph-C₃H₄)] (**7**) is formed as the main product, which was identified by independent synthesis and structure determination.^[12b] The excess of allylbenzene is isomerized to *trans*- β -methylstyrene by **7**.

In conclusion, the first neutral, three-coordinate alkylrhodium(i) complex with γ -C–H agostic stabilization of a 14-electron Rh center by a saturated alkyl ligand has been isolated and fully characterized. Its pronounced reactivity, which is based upon facile decoordination of the weakly bound hydrocarbon chain, makes it a suitable precursor for investigations of the d⁸-ML₃ chemistry of rhodium and of unsaturated alkylrhodium complexes; it models intermediates in, for example, bond activation, hydroformylation, or polymerization reactions.

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- [12] a) Single crystals were obtained by slowly concentrating a solution of **2** in Et₂O at –15 °C by solvent evaporation. Crystal dimensions 0.37 × 0.20 × 0.10 mm³, monoclinic, space group *P*2₁/*n*, *Z* = 4, *a* = 9.4062(1), *b* = 19.1825(1), *c* = 14.2169(2) Å, β = 92.462(1)°, *V* = 2562.85(5) Å³, ρ_{calcd} = 1.240 g cm^{–3}, 2θ_{max} = 55.0°, λ(MoKα) = 0.71073 Å, 0.3° ω scans, *T* = 200 K, 26061 reflections collected, 5883 unique, 4379 observed with *I* > 2σ(*I*). Corrections for absorption were applied (program SADABS), μ = 0.795 mm^{–1}, *T*_{min} = 0.75, *T*_{max} = 0.94. The structure was solved by Patterson methods and refined by full-matrix least-squares methods on *F*² (program SHELXTL (5.10)), 271 parameters refined.
- Np hydrogen atoms not localized but considered at calculated positions. Final agreement factors *R*(*F*) = 0.040, *wR*(*F*²) = 0.089 for observed reflections. Largest peak and hole in the final difference map: 0.70 and –0.70 e Å^{–3}. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-148676 (**2**), CCDC-148678 (**3**), CCDC-148677 (**6**), and CCDC-148679 (**7**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). c) Structural data for **5**: C. Meier, PhD thesis, Technische Universität München (Germany), **1991**.
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YBa₂Cu₃O_{6+δ} as an Oxygen Separation Membrane**

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High-*T_c* superconducting oxides exhibit fast oxygen transfer across the interface between gas and solid phase and diffusion in the bulk at elevated temperatures.^[1,2] This is of crucial importance to the fine-tuning of the superconductivity by intercalating oxygen into the oxides to oxidize the copper ions. The fast oxygen transport kinetics may also be used to develop oxygen-semipermeable dense membranes, which have potential applications in oxygen production and oxy-

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gen-based industrial processes.^[3, 4] When oxygen activity in the gas phase is greater than that in the bulk of the oxide, oxygen is intercalated into the oxide, and the reverse process occurs when the oxygen activity in the gas phase is less than that in the oxide. Therefore, upon applying a differential oxygen partial pressure p_{O_2} across the oxide membrane, a nonvanishing oxygen flux results and permeates from the high- to the low- p_{O_2} compartment; this results in separation of oxygen from oxygen-containing mixed gases. With $\text{Bi}_2\text{Sr}_2\text{CaCu}_2\text{O}_8$ as a dense membrane, an appreciable oxygen flux is obtained at elevated temperatures.^[5] This prompted us to examine the possibility of using $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ as an oxygen-permeable membrane.

The oxygen permeability of $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ was determined by using a permeation cell in which a dense oxide disk (1.2 mm thick and 1.2 cm in diameter) acts as a membrane (Figure 1). The chromatograms of the feed and permeate streams at 850 °C are shown in Figure 2. The permeate contains a significant amount of oxygen, while nitrogen is hardly detectable. This clearly demonstrates that $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ is permeable to oxygen but impervious to other gas components such as nitrogen. Further quantitative analysis revealed that the oxide allows oxygen to be transported at a rate of $3.1 \times 10^{-4} \text{ mol m}^{-2} \text{ s}^{-1}$ at 850 °C, and $2.0 \times 10^{-4} \text{ mol m}^{-2} \text{ s}^{-1}$ at 750 °C, under a relatively small oxygen

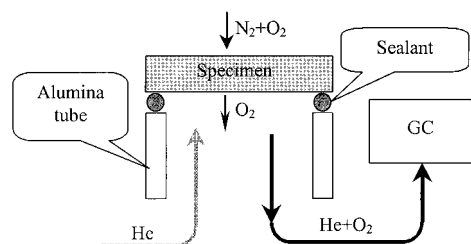


Figure 1. Schematic representation of a $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ -based permeation cell.

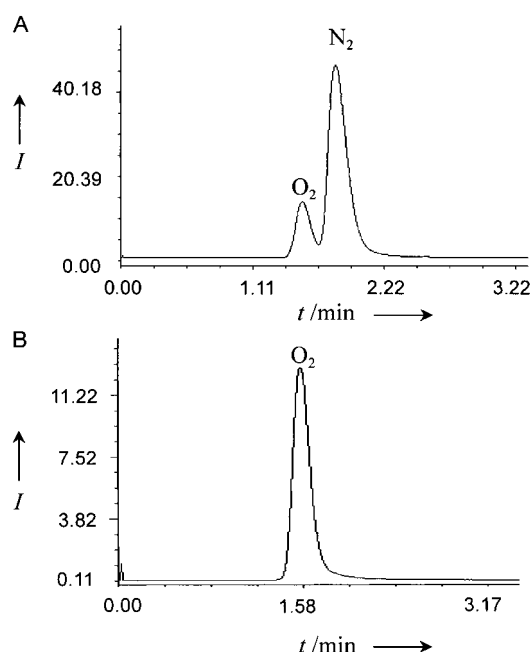


Figure 2. Chromatograms of A) feed stream (air) and B) permeated stream for the permeation cell. I = intensity.

partial pressure difference ($p_{\text{O}_2}(\text{high}) = 0.209 \text{ atm}$, $p_{\text{O}_2}(\text{low}) \approx 10^{-3} \text{ atm}$). Figure 3 shows the Arrhenius plot of the steady-state oxygen flux; the apparent activation energy is 44 kJ mol^{-1} . Compared with oxygen-deficient perovskite oxides such as $\text{La}_{1-x}\text{Sr}_x\text{CoO}_{3-\delta}$,^[6] the decrease in the oxygen permeability of $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ with decreasing temperature is less pronounced.

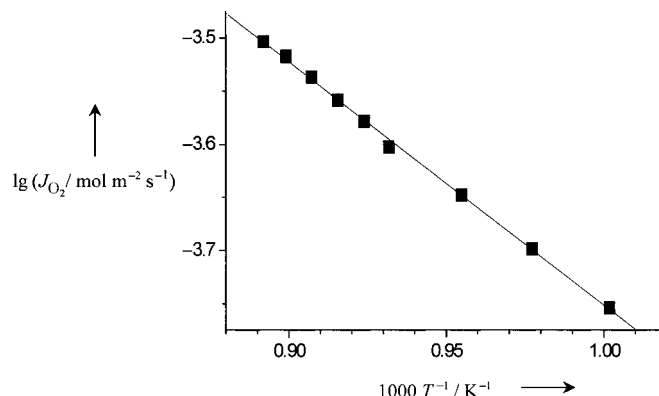


Figure 3. The temperature dependence of oxygen permeation flux through a $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ membrane of 1.2 mm thickness.

Oxygen permeation consists of two processes, namely, transfer of oxygen across the gas/solid interface and transport of oxygen in the bulk oxide membrane. The latter process is phenomenologically described by Fick's first law: $J_{\text{O}} = -D_{\text{chem}} \frac{\partial C_{\text{O}}}{\partial x}$. From the measurements of the oxygen permeation flux (J_{O_2}), J_{O} is available by virtue of $J_{\text{O}} = 2J_{\text{O}_2}$. The oxygen concentration gradient $\partial C_{\text{O}} / \partial x$ across the $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ membrane can be estimated by $\frac{\delta(\text{low}) - \delta(\text{high})}{V_{\text{m}} L}$, where $\delta(\text{low})$ and $\delta(\text{high})$ are the oxygen nonstoichiometry of the oxide corresponding to low and high oxygen partial pressure, respectively; V_{m} is the molar volume of the oxide, and L the thickness of the sample. From the oxygen nonstoichiometry data^[7] at $p_{\text{O}_2} = 0.209$ and 0.001 atm and the oxygen permeation flux from Figure 3, the oxygen chemical diffusion coefficient D_{chem} can be calculated. Figure 4 shows the Arrhenius plot for D_{chem} ; the apparent

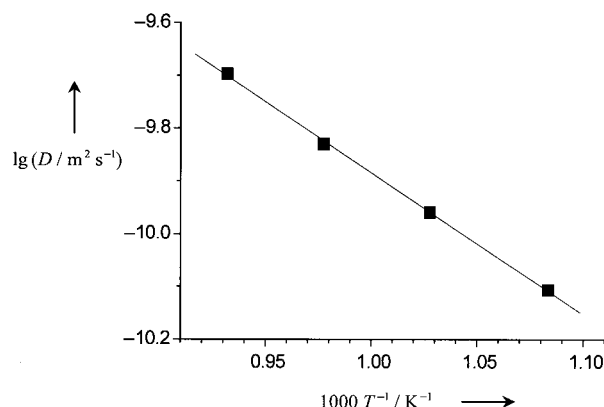


Figure 4. Temperature dependence of the chemical diffusion coefficient of oxygen for $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$.

activation energy is $(51 \pm 0.9) \text{ kJ mol}^{-1}$. The value of D_{chem} is in the order of $10^{-10} \text{ m}^2 \text{ s}^{-1}$ in the temperature range of $650\text{--}850^\circ\text{C}$, while the oxygen tracer diffusion coefficient, determined by the method of Rothman et al.,^[1] is in the order of $10^{-13} \text{ m}^2 \text{ s}^{-1}$. Hence, the thermodynamic factor in our case is around 10^3 . The oxygen diffusion coefficients reported in the literature are widely scattered,^[8] and our present data are comparable to those reported by Mitberg et al.^[2]

Oxygen diffusion in $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ is generally assumed to take place in the CuO basal plane. To examine this assumption, oxygen permeation measurements were performed on $\text{LaYBa}_2\text{Cu}_2\text{Ti}_2\text{O}_{11}$,^[9] which can be regarded structurally as derived from $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ by substitution of the CuO basal plane by a $\text{TiO}_2\text{--LaO--TiO}_2$ sheet. The oxygen permeability, if any, is too small to be detected (less than $10^{-6} \text{ mol m}^{-2} \text{ s}^{-1}$). The sharp difference in oxygen permeability between these two oxides suggests that the CuO basal plane is the structural origin of fast oxygen transport. It is known that at temperatures above about 650°C , oxygen atoms are equally distributed on O1 and O5 positions in the basal plane, the occupancy being $\delta/2$. It is likely that oxygen transport occurs by jumping between O1 and O5 positions. The oxygen flux should be proportional to the product of the mobility and concentration of the basal-plane oxygen atoms. As oxygen transport is a thermally activated process, lowering the temperature results in a lower mobility and hence a lower flux. However, the concentration of mobile oxygen increases with decreasing temperature and thus partially compensates the loss in mobility. These two opposing effects result in a weak temperature dependence of oxygen permeation flux. It is also known that grain boundaries can enhance the oxygen transport.^[10] Our work demonstrates the role of the CuO basal plane in transporting oxygen and can help to understand the effects of grain boundaries. If oxygen ions encounter grains oriented along the c axis, they will bypass the grains and travel through grain boundaries.

Oxygen in the basal plane of the $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ lattice has been suggested to have different oxidation states namely, O^0 , O^{1-} , and O^{2-} .^[8, 11, 12] Unlike the movement of O^{1-} and O^{2-} , that of O^0 does not contribute to the flow of electrical charge. Since relative contributions of neutral oxygen atoms and charged oxygen ions to oxygen permeation remain unknown, it is inappropriate to derive oxygen ionic conductivity from oxygen permeation data by using the Wagner equation.^[4, 13] Instead, we can only give a phenomenological treatment of oxygen transport in terms of Fick's first law. Note that to maintain electrical neutrality, the movement of oxygen ions O^{1-} and O^{2-} in the oxide must be accompanied by movement of electrons in the opposite direction, which is termed ambipolar diffusion.^[13] $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ should be very suitable for oxygen transport by an ambipolar mechanism, because Cu(1)O and Cu(2)O_2 planes in the lattice can conduct oxygen ions and electrons (holes), respectively.

In summary, $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ exhibits good oxygen permeability at elevated temperatures. Further research topics are clarifying the oxygen transport mechanism in relation to the structure, and improving the oxygen permeability by optimizing the composition and microstructure.

Experimental Section

Single-phase $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ samples were prepared by a standard ceramic method. Appropriate amounts of reagent-grade Y_2O_3 , BaCO_3 , and CuO powders were weighed, mixed in a mortar for 2 h, and calcined in air at 920°C for 24 h. The calcined powder was uniaxially pressed into compacts and sintered at 950°C for 24 h. The density of the sintered compacts was measured by the Archimedes method. The phase composition of the calcined and sintered sample was determined by X-ray diffraction with $\text{Cu}_{\text{K}\alpha}$ radiation ($D/\text{Max-}\gamma_{\text{A}}$, Rigaku).

Sintered $\text{YBa}_2\text{Cu}_3\text{O}_{6+\delta}$ disks with relative density greater than 90% were machined to 1.2 mm in thickness and 1.2 cm in diameter, and then sealed to an alumina tube at 860°C to form a permeation cell (see Figure 1). Air was fed into the upper compartment, and a stream of high-purity helium was introduced into the lower compartment to sweep away the permeated gas components. The gas compositions were analyzed by GC (Varian 3400). The oxygen permeation flux was calculated from the concentration of the oxygen in the effluent stream and the flow rate of the helium.^[14]

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C₆₀F₂₀: “Saturnene”, an Extraordinary Squashed Fullerene**

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In our program of fluorinating fullerenes by metal fluorides under vacuum followed by HPLC separation of the products, we have isolated and in many cases fully characterized the following: C₆₀F₂,^[1] C₆₀F₁₆,^[2] C₆₀F₁₈,^[3, 4] C₆₀F₃₆ (two isomers),^[5] C₆₀F_nO (*n* = 4, 6, 8),^[6] C₆₀F₁₈O (three isomers),^[7, 8] C₆₀F₁₈O₂ (seven isomers),^[9] C₆₀F₁₇CF₂CF₃,^[10] C₆₀F₁₇CF₃ (two isomers),^[10] forty-nine derivatives of [70]fullerene,^[11] C₇₆F_n (*n* = 36, 38, 40, 42, 44), C₇₈F_n (*n* = 38, 42), C₈₂F₄₄, C₈₄F₄₀, and C₈₄F₄₄.^[12] The success in this work is due to the high polarity of the fluorofullerenes, which results in the derivatives having significantly different retention times. Moreover, they have substantial solubility in both toluene and alkanes, which further facilitates the separations.

Many of these components have been formed through fluorination with K₂PtF₆ under vacuum at approximately 465 °C, the major product under these conditions being C₆₀F₁₈. During preparation of a larger amount of this material, we isolated many other components, including a number of ethers (oxahomofullerenes) and bis-ethers.^[7–9] One of the latter was accompanied by a shoulder peak of 75 min retention time which gave a mass spectrum showing the presence of C₆₀F₂₀ with the typical $-nF$ fragmentation pattern, but the amount was insufficient for further characterization.

Subsequently we have scaled-up the preparation through the use of an MnF₃/KF fluorinating mixture. Whereas fluorination of [60]fullerene with MnF₃ gives mainly C₆₀F₃₆,^[5] addition of an equimolar amount of KF reduces the overall fluorinating ability and gives greater yields of products with lower fluorine content, including C₆₀F₁₈ and C₆₀F₂₀. The isolated amount of the latter (1–2 mg) was sufficient for spectroscopic study and we now report its extraordinary structure.

C₆₀F₂₀ is off-white and with toluene forms only very pale lemon solutions, in contrast to other fluorofullerenes which give deeper lemon-yellow solutions. It has unusual solubility behavior, in that the pure material is very reluctant to redissolve in toluene, but eventually does so. This behavior is reminiscent of the behavior of pure C₆₀ towards, for example, hexane and may be attributed in both cases to close packing of the cages so that penetration of the lattice by the solvent is very slow.

The mass spectrum (Figure 1) shows the parent ion peak at 1100 amu, with a fragmentation pattern of regular loss of 20 F atoms (either singly or as pairs) down to C₆₀, showing the compound to be C₆₀F₂₀; the pattern is reminiscent of the behavior of C₆₀F₁₆^[2] and C₆₀F₁₈^[3] under EI conditions. The spectrum was duplicated precisely from a second sample.

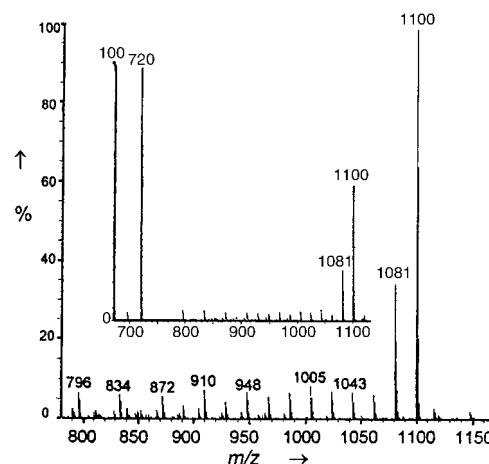


Figure 1. EI mass spectrum (70 eV) for C₆₀F₂₀ (inset shows full range).

The IR spectrum (KBr) (Figure 2) consists mainly of a single band at 1131 cm⁻¹ in the C–F stretching region indicative of a highly symmetrical structure. Small shoulder peaks to the main band are at 1206, 1183, 1162, 1111, 1102,

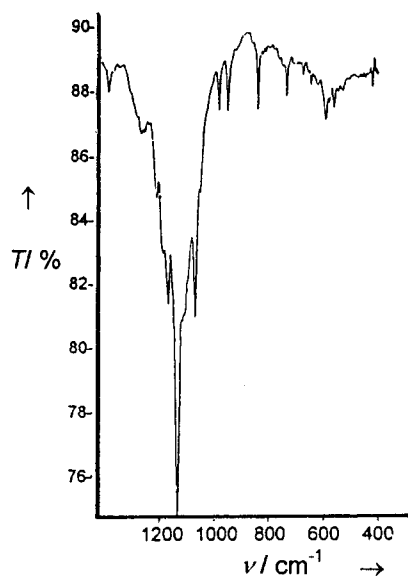


Figure 2. IR spectrum (KBr) of C₆₀F₂₀.

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1066, and 1047 cm^{-1} ; other minor peaks occur at 981, 951, 839, and 732 cm^{-1} .

The most outstanding spectroscopic feature is the single line ^{19}F NMR spectrum (Figure 3) at $\delta = -132.8$. This is as notable as the single line ^{13}C NMR spectrum obtained for C_{60} itself,^[13] and shows that all twenty fluorine atoms are equivalent.

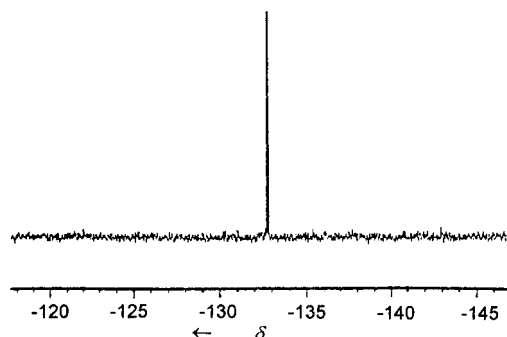


Figure 3. ^{19}F NMR spectrum (338.9 MHz) of $\text{C}_{60}\text{F}_{20}$.

The structure of the compound is shown in Figures 4a and 4b, and comprises two dehydrocorannulene caps held together by a $(\text{CF})_{20}$ chain; isostructural $\text{C}_{60}\text{H}_{20}$ was first described theoretically by Keppert and Clare.^[14] Figure 4c shows the structure as a Schlegel diagram ($\bullet = \text{F}$). d) The alternative structure for $\text{C}_{60}\text{F}_{20}$, ruled out by the mechanistic pathway.

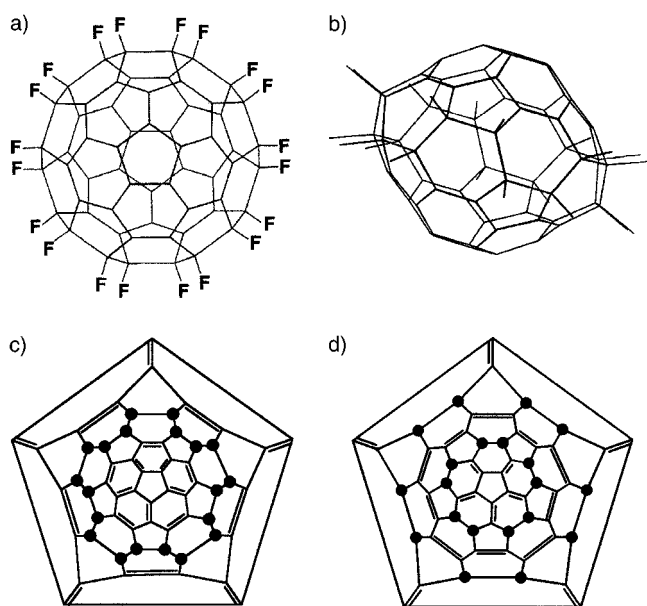
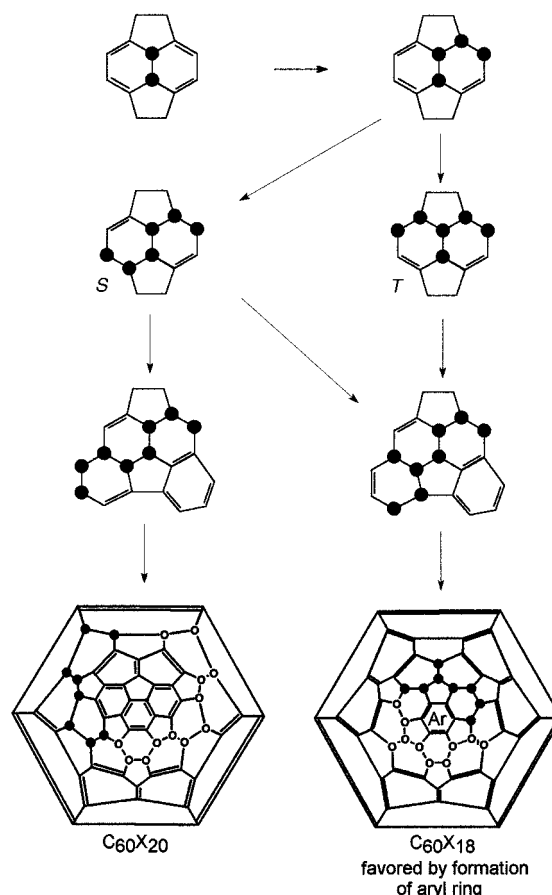


Figure 4. Structure of $\text{C}_{60}\text{F}_{20}$ (a) and its quite highly strained cage (b). c) $\text{C}_{60}\text{F}_{20}$ shown as a Schlegel diagram ($\bullet = \text{F}$). d) The alternative structure for $\text{C}_{60}\text{F}_{20}$, ruled out by the mechanistic pathway.

The molecule is quite highly strained, the extent of cage distortion being shown by the distances (MM3) of 6.29 Å (between the polar caps) and 7.85 Å (between sp^3 carbon atoms on opposite sides of the equator) compared to 6.83 Å in [60]fullerene itself. Thus the flattened poles and expanded equator is reminiscent of a spinning planet (Figure 4b), and the name “saturnene” commends itself in particular.^[15]

The calculated lengths (AM1) of the $\text{sp}^3\text{--sp}^3$ bonds are 1.69 (5:6 bond) and 1.58 Å (6:6 bond), the former being the longest is the most probable site (cf. [7]) for oxygen insertion. We have found mass spectrometric evidence for traces of the mono-, bis-, and trisoxides at 1116, 1132, and 1148 amu, respectively, in material tailing the main band. The length of the longest bond is the same as the longest bond in $\text{C}_{60}\text{F}_{18}$ (obs.: 1.672 Å;^[4] calcd (AM1): 1.69 Å^[7]).

In deducing a mechanism for the formation of $\text{C}_{60}\text{H}_{18}$ we argued that at a given stage in the contiguous addition pathway, two options were presented, one of which would lead to $\text{C}_{60}\text{H}_{18}$, the other to $\text{C}_{60}\text{H}_{20}$ (Scheme 1).^[16] Because of



Scheme 1. Mechanism of contiguous addition to [60]fullerene ($\text{X} = \text{F}, \text{H}$). Solid circles show the position of the addends in the precursor structure; open circles show the further addition sites giving the final structures (see text).

the strain present in the latter we suggested that its formation was less likely. The arguments apply equally to fluorination, and the fact that $\text{C}_{60}\text{F}_{20}$ is indeed formed under the same conditions that lead to $\text{C}_{60}\text{F}_{18}$, and moreover in about 5% relative yield is fully consistent with the mechanistic scenario. In Scheme 1, the initial contiguous addition to 1,2-difluoro-[60]fullerene leads to 1,2,3,4-tetrafluoro[60]fullerene. The next stage can give either 1,2,3,4,9,10-hexafluoro[60]fullerene (*S* pattern) or 1,2,3,4,11,12-hexafluoro[60]fullerene (*T* pattern). Further addition to either of these can lead ultimately to $\text{C}_{60}\text{F}_{18}$ (the further addition sites are indicated by open circles in the Schlegel diagram (Scheme 1)) a process strongly

avored by formation of the fully delocalized central aromatic ring. However, continuation of the zigzag addition to the *S* structure results only in the formation ultimately of $C_{60}F_{20}$.

There is only one possible alternative $C_{60}F_{20}$ structure that would give a single ^{19}F NMR line, and this has isolated pairs of fluorine atoms arranged as shown in Figure 4d. This can be ruled out because it cannot be formed by the contiguous addition mechanism which is now well established to apply in fluorination and also in hydrogenation.^[2, 3, 5, 6, 17] Moreover it has ten double bonds in pentagons (a destabilizing feature),^[18] whereas the structure in Figure 4a–c has none. This predicted instability is confirmed by the calculated heats of formation which are higher for the alternative structure by 80.2, 89.0, and 130.1 kcal mol⁻¹ (AM1, PM3, MNDO, respectively). The alternative structure is ruled out further by the EI mass spectrometric fragmentation pattern of $C_{60}F_{20}O$, which yields $C_{58}F_{17}^+$ and CF_3CO^+ . For elimination of the latter fragment, adjacency of three fluorine atoms is required.

An area of intensive current fullerene research concerns the construction of donor–acceptor derivatives likely to have photonic/photovoltaic applications, and this has been reviewed recently by Guldi.^[19] In these, the fullerene derivative is the acceptor, and the need is for enhancement of the electron withdrawal by the cage, thereby retarding back-electron transfer for the cage to the donor. Unfortunately, most donors make the cage less electron withdrawing by changing the hybridization state of some of the cage carbon atoms. However, the presence of many fluorine atoms on the cage increases the electron withdrawal, as indicated by the electron affinities (eV) of 4.05 ($C_{60}F_{44/46}$),^[20] about 3.48 ($C_{60}F_{36}$),^[21] and 2.74 ($C_{60}F_2$)^[22] compared to 2.65 for C_{60} .^[23] The reduction potential of $C_{60}F_{48}$ is also 1.38 V more positive than the first reduction potential of C_{60} .^[24] Electron withdrawal in $C_{60}F_{20}$ may be further aided by the strain such that the carbon atoms acquire greater *s* character. This is indicated by the downfield location of the ^{19}F NMR signal, relative to that for $C_{60}F_2$ ($\delta = -148.3$).^[1] Since there are two faces on the molecule for attachment of addends, one can envisage polymeric structures in which the donors are bonded to two $C_{60}F_{20}$ molecules, and so on. The molecule may thus prove to be an important synthon for such applications, and with this in mind we are seeking to improve the yield so that electrochemistry and other relevant experiments can be performed.

Experimental Section

$C_{60}F_{20}$ was isolated from the products of heating mixtures (ground intimately in a dry box) in a glass reactor under reduced pressure (1×10^{-3} mmHg); the mixtures comprised either [60]fullerene (240 mg) and Cs_2PbF_6 with heating at 580 °C for 6 h, or [60]fullerene (60 mg) and an equimolar KF/MNF_3 mixture (420 mg) with heating at 480 °C for 8 h. The products were extracted with toluene, filtered with exclusion of moisture, and separated by HPLC using a 10 mm $\times$ 25 cm Cosmosil Buckyrep column with elution by toluene at 4.7 mL min⁻¹. The main component ($C_{60}F_{18}$) eluted at 37 min, and $C_{60}F_{20}$ eluted at 74 min. The material of this latter retention time and obtained by either preparative method was spectroscopically identical.

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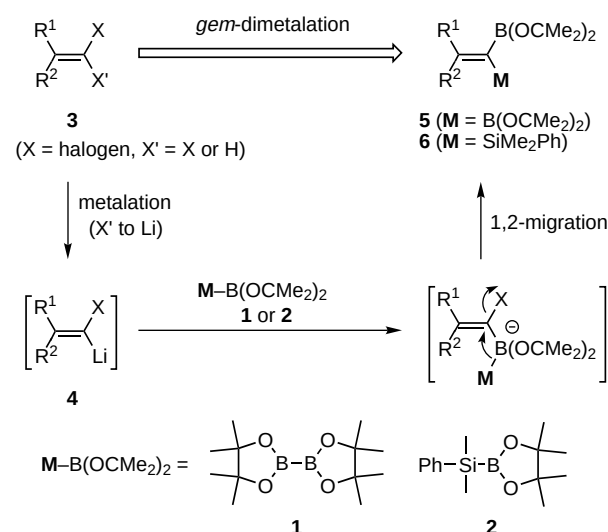
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Geminal Difunctionalization of Alkenylidene-Type Carbenoids by Using Interelement Compounds

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Interelement compounds contain either an interelement linkage or a homo-/heteroelement–element bond, and have recently been employed in the presence of a transition metal catalyst extensively for the functionalization of unsaturated carbon–carbon bonds.^[1] Thus, the same or different elements can be introduced into unsaturated substrates simultaneously and directly to give products having two metal– or heteroatom–carbon bonds that allow further elaborative synthetic transformations. The addition of a reagent with a B–B, Si–B, or Si–Si bond to unsaturated carbon–carbon bonds provides an especially attractive and straightforward method to directly introduce boryl and/or silyl groups into organic molecules by *vic*- or 1,4-diboration,^[2] silylboration,^[3] or disilylation.^[4]

Herein we report that bis(pinacolato)diboron (**1**)^[5] and (dimethylphenylsilyl)(pinacolato)borane (**2**)^[6] react with 1-halo-1-lithioalkenes **4**,^[7] alkenylidene-type carbenoids available from 1,1-dihaloalkenes or 1-haloalkenes **3**, to afford 1,1-diborylalkenes **5**^[8] or 1-boryl-1-silylalkenes **6**,^[9] respectively. These products are readily converted into tri- or tetra-substituted alkenes through various transition metal catalyzed carbon–carbon bond formations (Scheme 1).



Scheme 1. Geminal difunctionalization of alkenylidene-type carbenoids using interelement compounds.

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

Reagent **4a** was prepared by lithiation of (1,1-dibromomethylene)cyclohexane (**3a**) with butyllithium (1.05 mol) in THF/diethyl ether (2:1) at -110°C . Compound **1** (1.1 mol) was added to this solution at -110°C and the resulting mixture was stirred at -110°C for 10 min, gradually allowed to warm to room temperature, and stirred for 12 h (overnight). Work-up and chromatography (silica gel, hexane/ethyl acetate) gave 1,1-(diborylmethylene)cyclohexane **5a** in 93 % yield (Table 1, entry 1).^[10] Using **2** in place of **1**, we obtained 1,1-(boryl(silyl)methylene)cyclohexane **6a** in 75 % yield (Table 1, entry 2). We next applied the reaction to an unsubstituted carbenoid, 1-bromo-1-lithioethene (**4b**), available by

Table 1. Reaction of alkenylidene-type carbenoids with the diboron or silylborene reagent.

Entry	Substrate	Method ^[a] / Reagent ^[b]	Product ^[c]	Yield [%]
1		A/1		5a 93
2		A/2		6a 75
3		B/1		5b 91
4		B/2		6b 81
5		C/1		5c 89
6		C/2		6c ^[d] 75
7		D/1		5d 82
8		D/2		6d ^[d] 89
9		C/1		5e 48
10		C/2		6e ^[e] 49
11		E/1		5f 65
12 ^[f]		F/2		6f ^[d] 44

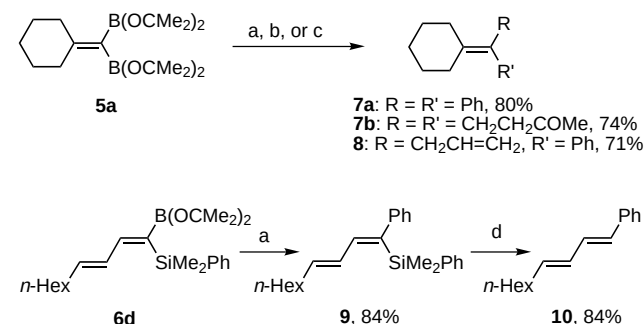
[a] A) BuLi (1.05 mol), THF/Et₂O (2:1), -110°C , 10 min. B) LiTMP (1.10 mol), THF/Et₂O (2:1), -110°C , 15 min. C) LiTMP (2.10 mol), THF, -90°C , 15 min. D) BuLi (1.05 mol), THF, -90°C , 15 min. E) BuLi (1.05 mol), THF/Et₂O (2:1), -110°C , 10 min. F) BuLi (0.95 mol), Et₂O, -110°C , 30 min. [b] **1** = [(Me₂CO)₂B]₂, **2** = PhMe₂Si–B(OCMe₂)₂. [c] M = B(OCMe₂)₂ for **5**; M = SiMe₂Ph for **6**. Yields of isolated product are given. [d] Single isomer. [e] *E/Z* = 1:1. [f] MEMO = CH₃OCH₂CH₂OCH₂O.

treatment of vinyl bromide (**3b**) with lithium 2,2,6,6-tetramethylpiperidine (LiTMP), and isolated 1,1-diborylethene **5b** (or **6b**) in high yields (Table 1, entries 3 and 4, respectively). As (*E*)-1,4-dihalo-2-butene is known to give predominately (*Z*)-1-halobutadiene,^[11] (*E*)-1,4-dichloro-2-butene (**3c**) was treated with two equivalents of LiTMP at -90°C to stereoselectively give (*Z*)-1-chloro-1-lithio-1,3-butadiene (**4c**),^[12b] which was allowed to react with **1** (or **2**) and afforded dienyldiborane **5c** (or dieny(silyl)borane **6c**) in high yields (Table 1, entries 5 and 6, respectively). Noteworthy is that the stereochemistry of **6c** was exclusively *E*^[13] in accord with the

configuration of **4c** and with a mechanism involving stereoselective formation of an intermediate borate complex followed by stereospecific 1,2-migration.^{[14], [15]} To extend the scope of the reaction, we treated **3d** with LiTMP, and **3e** with BuLi, to produce the conjugated alkylidene-type carbenoids **4d** and **4e**, respectively, which were subsequently treated with **1** (or **2**) to give rise to diene **5d** (or **6d**) and enyne **5e** (or **6e**), respectively (Table 1, entries 7–10). The stereochemistry (*Z*) of **6d** was completely controlled,^[13] whereas **6e** was isolated as a stereoisomeric mixture due probably to facile isomerization of carbenoid **4e**.^[12b] Stereoselective preparation of an alkylidene-type carbenoid is possible when a substrate contains a control element like an alkoxy group. For example, a stereoselective bromine–lithium exchange reaction takes place when 0.95–0.98 mol of BuLi is added to **3f** in diethyl ether at –110 °C.^[16] The resulting (*E*)-1-bromo-1-lithioalkene reagent **4f** was treated with **2** to afford **6f** as a single isomer (Table 1, entry 12).^[11] Similarly, the same substrate gave **5f** upon treatment with **1** (Table 1, entry 11).

These results clearly demonstrate that the *gem*-diboration and *gem*-silylboration reaction involve 1,2-migration of a boryl^[17] or silyl^[18] group with inversion of configuration.^[19] In particular, the configurations of **4f** and **6f** clearly demonstrate that lithium in (*E*)-**4f** was initially replaced by boron in **2** and then silyl migration took place with inversion of configuration.

The products **5** and **6** serve as potential substrates for the Miyaura–Suzuki coupling reaction.^[20] Coupling of **5a** with iodobenzene afforded 1,1-diphenylmethylenecyclohexane (**7a**; Scheme 2). Double conjugate addition of **5a** to methyl



Scheme 2. Miyaura–Suzuki coupling reaction of the resulting *gem*-bismetallated olefins. a) for **7a**: PhI (3 mol), [Pd(PPh₃)₄] (3 mol %), aq. KOH (6 mol), dioxane, 90 °C, 24 h. b) for **7b**: MVK (4 mol), [Rh(acac)(CO)₂]/dppb (6 mol %), MeOH/H₂O, 50 °C, 24 h. c) for **8**: 1) CH₂=CHCH₂Br (1 mol), [Pd(PPh₃)₄] (3 mol %), aq. KOH (3 mol), dioxane, 70 °C, 24 h; 2) PhI (1 mol), [Pd(PPh₃)₄] (3 mol %), aq. KOH (3 mol), dioxane, 70 °C, 24 h. d) TBAF (2 mol), THF, 60 °C, 2 h. acac = acetylacetonate, dppb = 1,4-bis(diphenylphosphanyl)butane, TBAF = tetrabutylammonium fluoride.

vinyl ketone (MVK) was catalyzed by a Rh complex to give 1,7-diketone **7b**.^[21] Stepwise coupling is also possible: allylation followed by phenylation of **5a** afforded **8** in a high overall yield. Similarly, **6d** coupled with iodobenzene to afford trisubstituted 1-silylalkene **9**, which after protodesilylation, gave (*E,E*)-diene **10** clearly demonstrating the stereochemical course of the sequence of reactions (Scheme 2).^[22]

In summary, lithium carbenoids **4** are shown to react with **1** or **2** successfully to afford 1,1-diborylalkenes **5** or 1-boryl-1-silylalkenes **6** stereoselectively. Synthetic elaborations of these alkenylborates are readily achieved for extension of the olefinic carbon framework.

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(50 MHz, CDCl₃): δ = 24.7, 26.4, 28.7, 37.4, 82.7, 171.5. IR: (nujol) 1615, 1320, 1285, 1265, 1245, 1220, 1140, 1105, 1010, 985, 965, 890, 855, 670 cm⁻¹; MS: *m/z* (%): 350 ([M⁺+2], 0.2), 349 ([M⁺+1], 2), 348 ([M⁺], 8), 347 ([M⁺ - 1], 4), 333 ([M⁺ - Me], 8), 291 (100); elemental analysis calcd for C₁₉H₃₄B₂O₄ (%): C 65.56, H 9.84; found: C 65.31, H 10.03.

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Nitroxide Radicals as Templating Agents in the Synthesis of Magnets Based on Three-Dimensional Oxalato-Bridged Heterodimetallic Networks**

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Building an extended compound with a particular crystal structure from molecular precursors in solution is still a challenge in many areas of chemistry.^[1] Coordination chemistry provides a useful algorithm for this purpose (lattice engineering) because coordination geometries are well defined by strong and highly directional bonds. This concept is especially relevant in the synthesis of molecular magnetic materials since metal complexes provide the spin carriers (metal ions) and ligands through which magnetic interactions can occur.^[2]

The ability of the oxalate (ox) ion, C₂O₄²⁻, to transmit efficiently magnetic interactions through its bridging mode has been well documented since the pioneering work on dinuclear copper(II) complexes.^[3] Later, the use of the homoleptic species [M(ox)₃]³⁻ (M = Cr^{III}, Fe^{III}) provided an easy access to systems of higher dimensionality.^[4] Only two families of high-dimensional oxalato complexes displaying magnetic order have been described: a) two-dimensional (2D) heterodimetallic compounds of formula A[M^{II}M^{III}(ox)₃] (A = quaternary onium cation, M = metal) with a honeycomb-layered structure^[5] and b) three-dimensional (3D) homometallic compounds of formula A[M₂^{II}(ox)₃] or A[M^{II}-M^{III}(ox)₃](ClO₄) (A = [M(bpy)₃]²⁺) with a cubic chiral packing.^[6] The resulting dimensionality depends on the type of A^{m+} ion used, so that these cations can be considered as *templating agents* for the overall structure.^[7] There is a fine interplay between molecular recognition and chirality in this kind of system: 2D structures are achiral but, within each layer, all the M^{II} sites have the same chirality while all the M^{III} sites have the opposite one; in the 3D systems, both sites adopt the same configuration. In all cases, the enantioselective synthesis of the optically active stereoisomers using chiral building blocks is possible.^[8] Besides their role as structure-directing agents, the A^{m+} ions can also introduce physical properties of interest to the magnetic system, leading to multiproperty materials. Along this line, we have synthesized a family of 2D compounds where the “innocent” quaternary onium cation has been replaced by redox-active species of the decamethylmetallocenium type^[9] or organic donors such as BEDT-TTF (2,2'-bis(5,6-dihydro-1,3-dithiolo[4,5-*b*][1,4]di-

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thiin)). The latter provided the first example of the coexistence of ferromagnetism and metal-like behavior in a molecular solid.^[10]

Nitronyl-nitroxides have been widely used in the preparation of molecular magnetic materials, either by themselves (*all-organic approach*)^[11] or as ligands in transition metal complexes (*metal-radical approach*).^[12] The preparation of cationic nitronyl–nitroxide radicals of the *N*-alkylpyridinium type introduced by Awaga and co-workers^[13] allowed the combination of these entities with simple paramagnetic anions.^[14] Kahn realized that it was possible to bridge heterodimetallic ordered chains using these cations and prepared the first molecule-based magnets containing three different spin carriers.^[15] To date, this is the only family of materials having this particularity.

This prompted us to investigate the synthesis of extended dimetallic oxalato complexes of the type $\text{rad}^+[\text{M}^{\text{II}}\text{Cr}(\text{ox})_3]^-$ ($\text{rad}^+ = 2-(1\text{-methylpyridinium-4-yl})-4,4,5,5\text{-tetramethylimidazoline-1-oxyl-3-oxide}$). They can be obtained by reaction of $(\text{rad})_3[\text{Cr}(\text{ox})_3]^-$ with the appropriate divalent metal salt. One such compound, $\text{rad}^+[\text{Mn}(\text{H}_2\text{O})\text{Cr}(\text{ox})_3]^- \cdot 2\text{H}_2\text{O}$ (**1**), is based on a cationic nitronyl–nitroxide free radical (rad^+) that acts as a templating agent in the formation of a 3D dimetallic oxalato network. Compound **1** crystallizes in the monoclinic C_c space group. The molecular structure of rad^+ (Figure 1a) is very similar to that found in the previously reported salts. Figure 2 shows the packing of the radicals in the *bc* plane. Note the formation of zigzag chains running along the *z*-axis. The shortest contact between proximate radicals within the chain is $\text{O2} \cdots \text{C10}(x, 1-y, z-\frac{1}{2})$: 4.312(5) Å. The N–O functions are well isolated from each other: the minimum O $\cdots$ O intermolecular distance also corresponds to two adjacent radicals in the chain ($\text{O1} \cdots \text{O2}(x, 1-y, z-\frac{1}{2})$: 6.891(5) Å). This is in contrast with the situation found in most crystals of nitroxide radicals, where O $\cdots$ O contacts of about 3.5 Å are observed.

The oxalato network is also shown in Figure 2 to stress the role of the free radicals as structural directors. The zigzag chains of radicals find their replica in the inorganic lattice. Indeed, the packing of the 3D dimetallic network can be viewed, in a first step, as zigzag alternating Mn–Cr chains oriented in the same direction (continuous bonds). A detailed picture of this one-dimensional fragment is shown in Figure 3, where the linkage between adjacent metal ions by bisbidentate μ -oxalate bridges is clearly seen. Noteworthy is that the chirality of the metal centers follows the sequence $\cdots \Delta \Delta \Delta \Delta \Delta \Delta \cdots$ along the chain. This implies the existence of two distinct bisbidentate bridges: one connecting metal centers of the same chirality ($\text{Mn1} \cdots \text{Cr1}$: 5.421(3) Å) and a second one connecting centers of opposite chirality ($\text{Mn1} \cdots \text{Cr1}(x, 2-y, z+\frac{1}{2})$: 5.3927(16) Å).

The chains are linked between them through a new type of oxalate bridge (see Figure 1b) that is simultaneously bidentate (towards chromium) and monodentate (towards manganese). A water molecule occupies the vacant position in the coordination sphere of the Mn^{2+} center. References in the literature concerning this unusual bridging mode are very scarce.^[16, 17] In our complex, the linkage (dashed bonds in Figure 2) takes place between a $\text{Cr}(\text{ox})_3$ building block and a

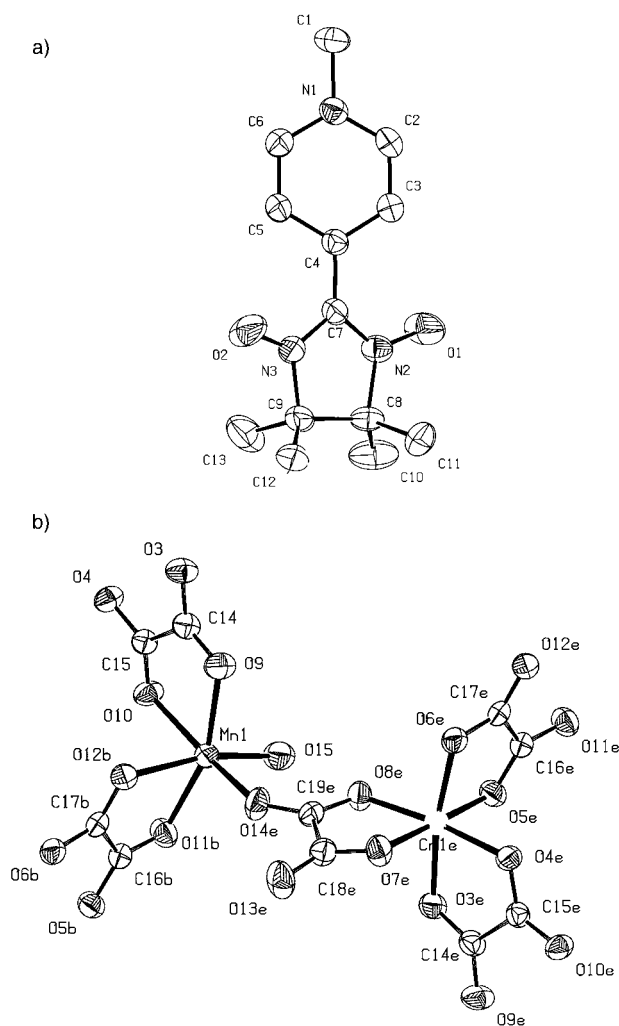


Figure 1. Molecular structure of a) rad^+ and b) $[\text{Mn}(\text{H}_2\text{O})\text{Cr}(\text{ox})_3]^-$ (ellipsoids are set at the 50% probability levels; all H atoms have been omitted for clarity). Selected distances [Å] and angles [°]: a) N2–O1 1.271(3), N3–O2 1.271(3); C3–C4–C7–N2 26.6(4); b) Mn1–O15 2.138(2), Mn1 $\cdots$ Cr1e ($x+\frac{1}{2}, \frac{1}{2}-y, z+\frac{1}{2}$): 5.5977(14).

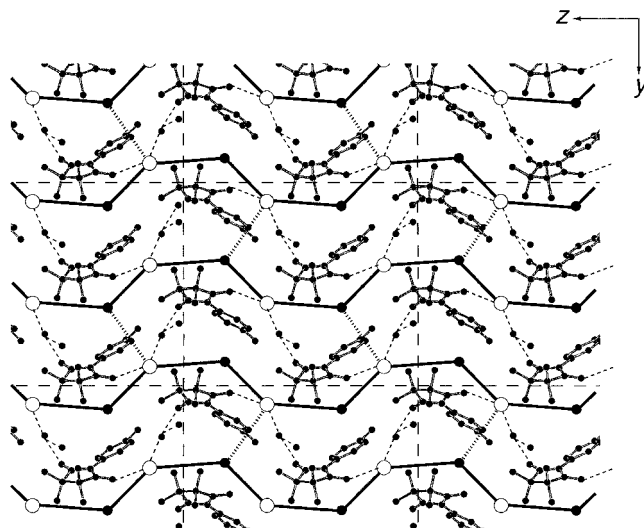


Figure 2. Projection of the crystal structure of **1** onto the *bc* plane (oxalate anions have been omitted for clarity). Thick bonds replace oxalate bridges: bisbidentate (continuous bonds) and bidentate/monodentate, whereas dashed lines (---) represent hydrogen bonds, broken lines (---) the unit cell grid, ○ = Mn, ● = Cr.

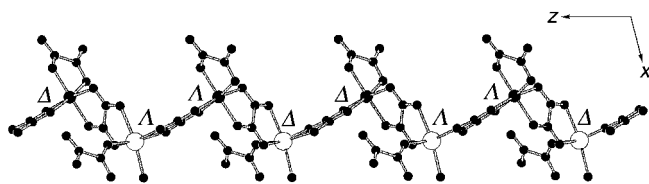


Figure 3. View along the *b* axis of the oxalato-bridged Mn–Cr ferromagnetic chains. The absolute configuration of the building blocks is also shown.

Mn(ox)₃(H₂O) unit of opposite chirality. This results in the formation of an *achiral* 3-connected 10-gon network. Out of this plane, the decagonal units are arranged in such a way that helical hexagonal channels are formed. Since the resulting network is achiral, both types of helix are found in the structure (Figure 4).

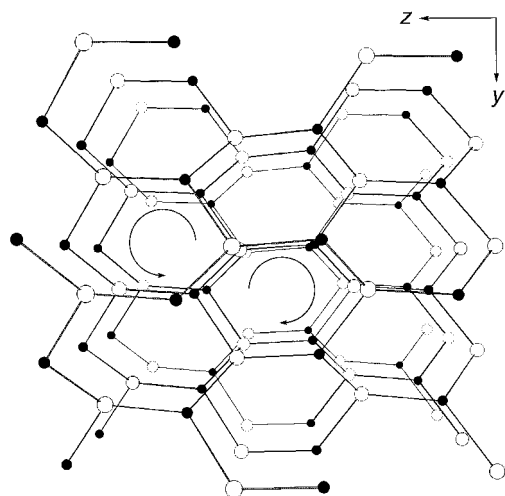


Figure 4. Perspective view along the *a* axis of the heterometallic lattice of **1** showing the metal connectivity and the helical channels formed; ○ = Mn, ● = Cr.

The water molecules of crystallization are linked to each other (O17...O16 (*x* + 1, *y*, *z*): 2.762(4) Å) and hydrogen bonded to the coordinated water molecule (Mn1–O15...O17: 2.674(4) Å). Short hydrogen bonds (Figure 2) are also found between the nitroxide oxygen atoms and the coordinated water molecules (Mn1–O15...O2–N3 (*x* + ½, ½ – *y*, *z* + ½): 2.733(4) Å; O17...O1–N2: 2.800(3) Å). Thus, the radicals are tightly bound to the inorganic lattice by means of an extended hydrogen-bonded network.

Magnetic susceptibility (χ) measurements have been made on **1**. Figure 5 shows the thermal dependence of χT (the product of molar magnetic susceptibility with temperature) and χ . The χT has a constant value from room temperature down to 100 K (χT = 6.55 emu K mol^{–1}). Below this temperature, χT increases on cooling and reaches a maximum at 18 K, where it equals 7.15 emu K mol^{–1}. Then, χT drops abruptly and has a value of 1.5 emu K mol^{–1} at 2 K. The temperature dependence of χ shows a sharp maximum at 6 K with a typical Curie tail at lower temperatures.

At room temperature, the observed value of χT is approximately equal to the sum (χT = 6.625 emu K mol^{–1}) of

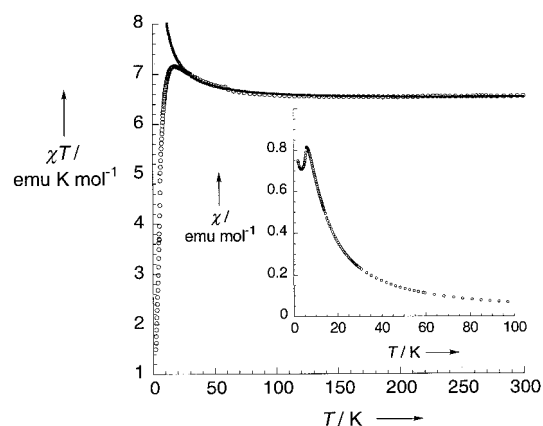


Figure 5. Thermal variation of the χT product (open circles) for **1**. The solid line represents the best-fit calculated data. Inset: Temperature dependence of χ .

the expected contributions corresponding to the three isolated spin carriers (nitroxide radical ($S = \frac{1}{2}$), Mn²⁺ ($S = \frac{5}{2}$), and Cr³⁺ ($S = \frac{3}{2}$) cations). The sharp maximum observed in the χ versus *T* curve is characteristic of a long-range antiferromagnetic ordering. At temperatures above the transition, the magnetic behavior points to the presence of a low-dimensional system with dominant ferromagnetic interactions. Taking into account these considerations, the thermal variation of the χT product has been analyzed in terms of a regular AB chain model^[18] with classical spins $S_A = \frac{1}{2}$ and $S_B = \frac{3}{2}$. The best-fit value for the exchange coupling constant (H_{ex}) is $J/k = +0.8$ K ($H_{\text{ex}} = -J \sum S_{\text{Ai}} S_{\text{Bi}}$). All previous studies indicate that the Mn^{II}–Cr^{III} exchange coupling through bisbidentate oxalate is ferromagnetic and, according to its structural features, the spin topology of **1** is best described in terms of ferromagnetic chains. An antiferromagnetic interaction between the chains should be present to account for the antiferromagnetic ordering observed at low temperatures. This interaction is certainly transmitted through the bidentate/monodentate oxalate anion. The lower symmetry of this bridge decreases the efficiency of the ferromagnetic pathway (as compared to the bisbidentate ligand) and the antiferromagnetic interaction becomes dominant, as has been shown recently in a chromium–manganese tetramer.^[17] Note that the presence of a Curie tail at very low temperatures can be explained by considering the paramagnetism of an isolated nitroxide radical ($S = \frac{1}{2}$). This indicates that the free radicals are not coupled to the metal centers, so that in the present example an antiferromagnetically ordered network coexists with a paramagnetic one. This is observed despite the fact that the nitroxide oxygen atom is hydrogen-bonded to the coordinated water molecule and, consequently, close to the manganese center (Mn1...O2 (*x* + ½, ½ – *y*, *z* + ½): 3.8510(27) Å). It seems that the exchange interaction through this bridge is too weak to be appreciated in the temperature range of the experiment. An example of oxalato-based dimetallic magnets incorporating other uncoupled paramagnetic species, such as the decamethylferricinium cation, is known in the 2D family.^[9]

The synthesis of molecular-based ferromagnets of this family can be anticipated by simply replacing Mn^{II} by Ni^{II}.

Owing to simple orbital symmetry considerations, this change should strengthen the ferromagnetic contribution from the bidentate/monodentate oxalate anion. In fact, our preliminary results on the analogous $\text{rad}[\text{NiCr}(\text{ox})_3]$ species shows that this compound is a ferromagnet with a critical temperature $T_c = 16$ K and a coercive field of 4000 Oe.

To summarize, the present report introduces the use of free radicals as counterions of an extended lattice. This is an efficient strategy for the synthesis of hybrid two-network magnetic materials based on organic free radicals and polymeric transition metal complexes. In the present case, nitroxide radicals act as templating agents in the formation of a unique three-dimensional oxalato-bridged heterometallic network. New molecular-based magnets with three different spin carriers have been obtained. This opens new synthetic pathways for novel and more complicated magnetic lattices.

Experimental Section

The cationic free radical prepared^[13] as an iodide salt (100 mg, 0.26 mmol) was added to a suspension of $\text{Ag}_2[\text{Cr}(\text{ox})_3]$ in EtOH (5 mL). After 30 min stirring, AgI was removed by filtration and a solution of $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (32 mg, 0.088 mmol) in the minimum amount of water was added to the filtrate. The resulting green suspension became clear after addition of H_2O (2 mL) and the mixture was left undisturbed in the dark. Green single crystals of **1** suitable for X-Ray structure analysis^[19–21] grew within a few hours. IR(KBr): $\tilde{\nu} \sim 1376$ (N–O), 1140 cm^{-1} (N–O).

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Synthesis and Characterization of $[\text{Sn}_8(2,6\text{-Mes}_2\text{C}_6\text{H}_3)_4]$ (Mes = 2,4,6-Me₃C₆H₂): A Main Group Metal Cluster with a Unique Structure**

Barrett E. Eichler and Philip P. Power*

Most polyhedral compounds with heavier Group 14 element frameworks fall into one of two broad categories; the Zintl anions E_n^{m-} ,^[1] and the substituted species of the formula E_nR_m ,^[2] which are accessible through the use of sterically demanding organic (R) groups. Several structural types are known for the latter category^[2] which extend from the simplest tetrahedrane cluster E_4R_4 , through trigonal-prismatic, cubic, and pentagonal-prismatic clusters E_6R_6 , E_8R_8 , and $\text{E}_{10}\text{R}_{10}$, respectively. A range^[2] of alkyl, aryl, and silyl^[3] ligands has been used to stabilize these frameworks. Recently, it has been shown that sterically crowding terphenyl ligands can limit the degree of aggregation in these clusters to $n = 2$ or 3 as in the dimeric alkynelead analogue $[\text{Pb}_2(2,6\text{-Trip}_2\text{C}_6\text{H}_3)_2]$ ^[4a] (Trip = 2,4,6-*i*Pr₃C₆H₂) or the trimeric germanium radical species $[\text{Ge}_3(2,6\text{-Mes}_2\text{C}_6\text{H}_3)_3]$ ^[4b] (Mes = 2,4,6-Me₃C₆H₂). The different degrees of aggregation in these two molecules can be rationalized on the basis of the different sizes of germanium and lead as well as the different steric requirements of their terphenyl substituents. These data also suggested that the use of the smaller 2,6-Mes₂C₆H₃ aryl ligand in conjunction with tin might result in the isolation of the elusive tetrahedrane cluster Sn_4R_4 . Herein we show that the attempted preparation of such a species by a coupling reaction of the aryltin halide $[\{\text{Sn}(\mu\text{-Cl})(2,6\text{-Mes}_2\text{C}_6\text{H}_3)_2\}]_2$ with potassium led not to the expected tetrameric product but to the species $[\text{Sn}_8(\text{C}_6\text{H}_3-2,6\text{-Mes}_2)_4]$ (**1**), featuring a novel main group element cluster framework which may represent a real structure along the decomposition pathway of Sn_nR_n clusters toward metallic tin.

Compound **1** was synthesized as purple crystals in 38% yield by reduction of $[\{\text{Sn}(\mu\text{-Cl})(2,6\text{-Mes}_2\text{C}_6\text{H}_3)_2\}]_2$ ^[5] with a slight excess of potassium in THF. It was characterized by ¹H, ¹³C, and ¹¹⁹Sn NMR spectroscopy, UV/Vis spectroscopy, and by X-ray crystallography.^[6] A thermal ellipsoid drawing (Figure 1) illustrates the crowded environment provided by the ligands. Figure 2 shows that the eight tin atoms of the Sn_8 core are arranged as a distorted rhombic prism with approximate D_{2h} symmetry. The Sn_8 array may also be thought of as a grossly distorted cubane structure if the long (3.107(2) Å) Sn(2)–Sn(3) and Sn(2A)–Sn(3A) bonds are uncoupled. It can be seen that only four of the tin atoms carry organic substituents. A similar ratio of organic groups to metal atoms was observed in the cubane cluster $[\text{In}_8\{2,6\text{-Mes}_2\text{C}_6\text{H}_3\}_4]$,^[7] but in that compound the four organic groups are attached to alternating corners of an In_8 distorted cubane array with D_{2d} point symmetry rather than to adjacent metal atoms

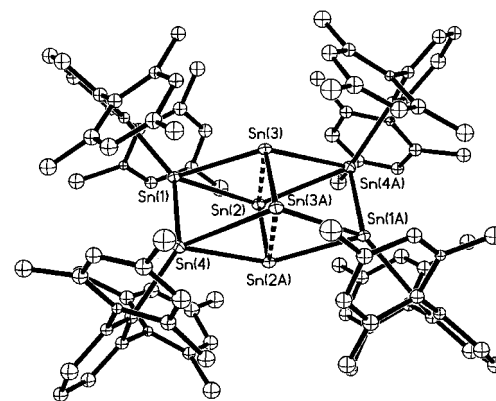


Figure 1. Structure of **1** (thermal ellipsoid (30%) plot without H atoms) illustrating the crowding nature of the 2,6-Mes₂C₆H₃ substituents.

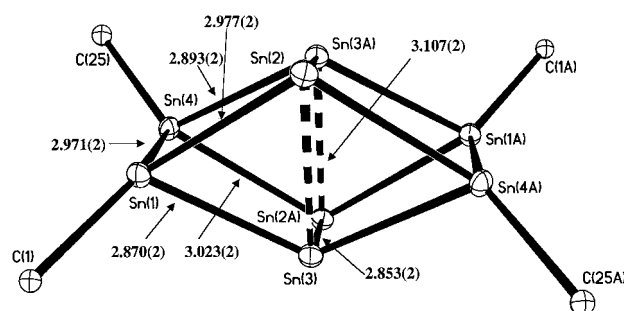


Figure 2. Structure of the core tin and *ipso*-carbon atoms of **1** (thermal ellipsoid (30%) plot) showing the tin–tin distances [Å]. Important angles [°]: C(1)–Sn(1)–Sn(3) 112.4(4), C(1)–Sn(1)–Sn(4) 127.9(4), Sn(3)–Sn(1)–Sn(4) 79.70(4), C(1)–Sn(1)–Sn(2) 131.9(4), Sn(3)–Sn(1)–Sn(2) 64.16(4), Sn(4)–Sn(1)–Sn(2) 99.62(5), Sn(3A)–Sn(2)–Sn(1) 77.94(4), Sn(3A)–Sn(2)–Sn(4A) 79.10(4), Sn(1)–Sn(2)–Sn(4A) 112.38(5), Sn(3A)–Sn(2)–Sn(3) 65.32(4), Sn(1)–Sn(2)–Sn(3) 56.24(4), Sn(4A)–Sn(2)–Sn(3) 56.30(4), Sn(2A)–Sn(3)–Sn(1) 103.61(5), Sn(1)–Sn(3)–Sn(4A) 119.80(6), Sn(2A)–Sn(3)–Sn(2) 114.68(4), Sn(1)–Sn(3)–Sn(2) 59.60(4), Sn(4A)–Sn(3)–Sn(2) 60.39(4), Sn(3A)–Sn(4)–Sn(1) 77.42(4), Sn(3A)–Sn(4)–Sn(2A) 63.31(4), Sn(1)–Sn(4)–Sn(2A) 97.23(4).

as in **1**. It seems that four 2,6-Mes₂C₆H₂ groups provide the appropriate amount of surface coverage to stabilize the eight metal core in both cases. The Sn–Sn distances fall in the range 2.853(2)–3.107(2) Å which is comparable to the range observed in Sn_nR_n clusters^[2, 9] and Zintl anions such as Sn_9^{4-} .^[10] For example, average Sn–Sn distances of 2.89(2) and 2.86(2) Å have been reported for the species $[\{(\text{thf})_2\text{Na}\}_2\text{Sn}_8\{\text{Si}(\text{iBu})_3\}_6]$ ^[11] and $[\text{Sn}_5(2,6\text{-Et}_2\text{C}_6\text{H}_3)_6]$,^[12] respectively. The tin–carbon distances of 2.22(2) and 2.28(2) Å are within the normal range.^[13] The distortions in the structure are apparent from the selection of angles given in the legend to Figure 2.

The bonding in **1** may be considered in a number of ways. One possibility is that it consists of a central unit of four Sn atoms (Sn(2), Sn(3), Sn(2A), Sn(3A)) which is complexed by two R–Sn(1)–Sn(4)–R and R–Sn(1A)–Sn(4A)–R fragments. In this model, the planar, rhombic Sn_4 core (Sn(2)–Sn(3)–Sn(2A) 114.68(4)°, Sn(3)–Sn(2)–Sn(3A) 65.32(4)°) involves single bonding between four divalent tin atoms (each with a lone pair), which are bound on each side of the Sn_4 plane by the RSnSnR units. The latter moieties bear little resemblance to a “distannyne” suggested by the alkyne-like formula; however,

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the Sn–Sn distance of 2.971(2) Å is longer than the normal tin–tin single bond of 2.80 Å found in gray tin.^[14] Moreover, the torsion angle for the C(1)–Sn(1)–Sn(4)–C(25) unit is 85.0°. The average Sn–Sn bond length (including the diagonal Sn(2)–Sn(3) and Sn(2A)–Sn(3A) distances) is very similar at about 2.96(7) Å and suggests that the formal Sn–Sn bond order in the cluster is less than one. The lower bond order is consistent with electron counting for the metal framework bonding. Thus, each of the four unsubstituted tin atoms, if they bear a lone pair of electrons, supplies two electrons, and the four RSn moieties each supply three electrons for a total of twenty electrons available for framework bonding or an average bond order of about 0.7 if fourteen Sn–Sn bonds are assumed. It is also possible to consider the Sn₈ core as a very distorted cube by uncoupling the relatively long Sn(2)–Sn(3) and Sn(2A)–Sn(3A) bonds. However, the acute angles (ca. 64°) at Sn(1), Sn(4), Sn(1A), Sn(4A) opposite these bonds seem to favor the existence of Sn(2)–Sn(3) and Sn(2A)–Sn(3A) interactions (as indicated by the dashed lines in Figure 2).

The ¹H and ¹³C NMR spectra of **1** display peaks typical for a 2,6-Mes₂C₆H₃-substituted species with the expected low-field shift (δ = 174.04) for the *ipso*-carbon atom of the central ring of the terphenyl group. The ¹¹⁹Sn {¹H} NMR spectrum of **1** features two signals at δ = 751.7 and 483.1 that are attributable to two different types of tin center. The lowest field signal at δ = 751.7 displays two sets of ¹¹⁷Sn/¹¹⁹Sn satellites due to coupling (¹J_{Sn,Sn} = 5.005 and 2.625 Hz) to two distinct tin centers. Moreover, the satellites display a 1:2 intensity ratio suggesting that this signal can be assigned to the tin atoms that carry organic groups since these tin centers are bound to one substituted and two equivalent unsubstituted tin centers. The more upfield peak at δ = 483.1 also displays two sets of satellite peaks (¹J_{Sn,Sn} = 5.005 and 4.098 Hz) that have equal intensities which can be assigned to the unsubstituted tin atoms since these tin centers are bound to two substituted and two unsubstituted tin centers. In addition, ¹¹⁹Sn NMR spectroscopy of the reaction mixture used to synthesize **1** showed other, less intense, peaks (e.g., at δ = 126.9, 8.5, –335, –390.5) indicating that at least one other tin cluster is present in the crude reaction mixture.^[15] Attempts to structurally characterize these and other Group 14 clusters are in progress.

Experimental Section

Under anaerobic and anhydrous conditions THF (40 mL) was added to a flask charged with potassium (0.33 g, 8.4 mmol) and [(Sn(μ -Cl)(2,6-Mes₂C₆H₃))₂]^[5] (3.27 g, 3.50 mmol). The yellow solution was heated until the potassium became molten at which point the solution rapidly turned red. The reaction mixture was allowed to cool to room temperature and

upon stirring for 14 h it had assumed a purple color. The solvent was then removed under reduced pressure and the purple residue was extracted with benzene (30 mL). The solution was filtered and the volume was reduced to about 20 mL. Storing the flask at ca. 6 °C overnight afforded the product **1** as purple crystals. Yield: 0.77 g, 0.33 mmol, 38%; m.p. 215–218 °C; elemental analysis calcd for Sn₂C₂₄H₂₅ (%): C 53.33, H 4.57; found: C 53.76, H 4.23; UV/Vis (hexanes): λ_{max} [nm] (ϵ) [M^{–1}cm^{–1}]: 307 (11 000), 522 (1460); ¹H NMR (C₆D₆, 399.77 MHz, 25 °C): δ = 1.91 (brs, 6H; *o*-CH₃), 2.00 (brs, 6H; *o*-CH₃), 2.30 (brs, 6H; *p*-CH₃), 6.75 (brs, 4H; *m*-Mes), 6.87 (d, 2H, ³J = 7.4 Hz; *m*-C₆H₃), 7.08 (t, 1H, ³J = 7.4 Hz; *m*-C₆H₃); ¹³C{¹H} NMR (C₆D₆, 100.53 MHz, 25 °C): δ = 21.57 (*o*-CH₃), 21.64 (*o*-CH₃), 22.79 (*p*-CH₃), 127.29 (*m*-Mes), 128.53 (*m*-Mes), 128.68 (*p*-C₆H₃), 129.39 (*m*-C₆H₃), 135.94 (*o*-Mes), 136.07 (*o*-Mes), 136.83 (*p*-Mes), 141.16 (*ipso*-Mes), 147.66 (*o*-C₆H₃), 174.04 (*ipso*-C₆H₃); ¹¹⁹Sn{¹H} NMR (C₆D₆, 149.16 MHz, 25 °C): δ = 751.7 and 483.1.

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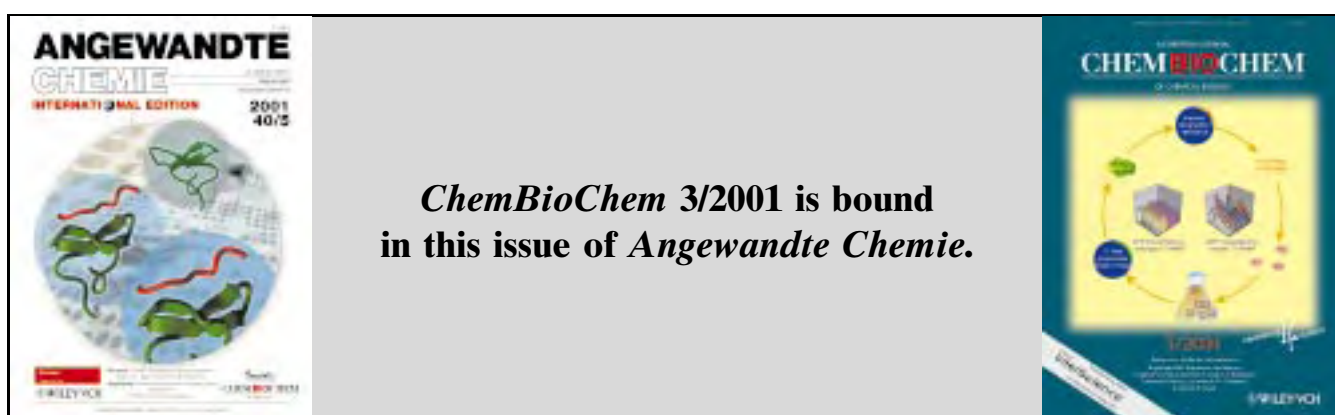
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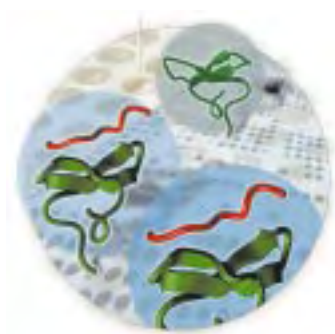
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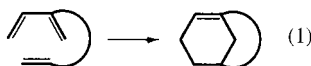
COVER PICTURE

The cover picture shows an array of several hundred synthetically produced variants of the 44 amino acids comprising the hyAP-WW protein domain. The array was produced by a stepwise SPOT synthesis on a cellulose membrane. At each synthesis site (spot) a WW domain is bound to the membrane through a C-terminal ester bond. The secondary structure of the WW domain is shown in green as a ribbon. The domains of the single spots differ only by a single amino acid. All the domains were tested simultaneously for their ability to bind to a peptide motif (red) common to many proteins. The binding was evident when visualized by chemoluminescence, with the Spots having various intensities. The systematic analysis undertaken here enabled molecular biology to be carried out that would have otherwise have required great effort, or not been done at all. This chemical technique also allows the construction of many non-genetically coded building blocks. Through the use of modern synthetic techniques for the coupling of peptides this method should also allow the synthesis of proteins. The combination of molecular biological and chemical methods opens up opportunities for the preparation of protein chips for diagnostics and drug discovery. More about this can be found in the article by Schneider-Mergener et al. on p. 897ff.



From chemical curiosities to highly sought synthetic building blocks: Anti-Bredt alkenes are accessible in one step from acyclic precursors by using the type 2 intramolecular Diels–Alder (IMDA) reaction described herein [Eq. (1)]. Unlike with the normal Diels–Alder reaction this variant allows high regio- and stereoselectivities. This provided the prerequisite for bridgehead alkenes to play a key role in the synthesis of a large number of complex natural products. Medium-sized rings are also readily accessible by using this method, and the bridges can be selected such that they can be cleaved after the synthesis.

Angew. Chem. **2001**, *113*, 864–894



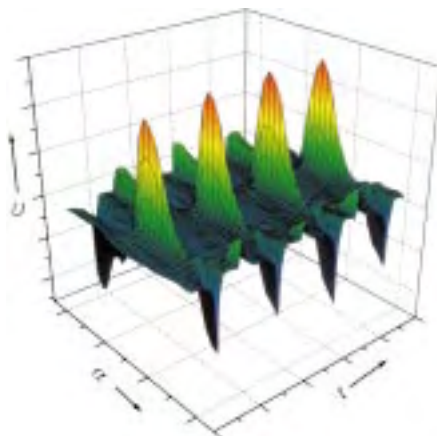
B. R. Bear, S. M. Sparks,
K. J. Shea* 820–849

The Type 2 Intramolecular Diels–Alder Reaction: Synthesis and Chemistry of Bridgehead Alkenes

Keywords: bridgehead alkenes • cycloaddition • natural products • strained molecules • synthetic methods

Spontaneous formation of ordered reactivity patterns at the electrode/electrolyte interface can occur in a variety of electrochemical reactions. Depending on the reaction conditions, different modes of spatial couplings necessary for cooperative behavior become dominating. This variability explains many of the multifaceted, spatiotemporal structure formations observed. The picture shows the spatiotemporal evolution of the potential at a Pt electrode during the oxidation of H_2 in the presence of Cu^{2+} and Cl^- ions after subtraction of the homogeneous oscillating part.

Angew. Chem. **2001**, *113*, 842–863



K. Krischer,* N. Mazouz,
P. Grauel 850–869

Fronts, Waves, and Stationary Patterns in Electrochemical Systems

Keywords: autocatalysis • electrochemistry • nonlinear dynamics • pattern formation • self-organization

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>

Formation of Super Wires of Clusters by Self-Assembly of Transition Metal Cluster Anions with Metal Cations

Highly Efficient and Ultrafast Phototriggers for cAMP and cGMP by Using Long-Wavelength UV/Vis Activation

Isolation and Structural Characterization of the Endohedral Fullerene $Sc_3N@C_{78}$

Synthesis of Conformationally Locked Carbohydrates: A Skew-Boat Conformation of L-Iduronic Acid Governs the Antithrombotic Activity of Heparin

The First Phosphine Oxide Ligand Precursors for Transition Metal Catalyzed Cross-Coupling Reactions: C–C, C–N, and C–S Bond Formation on Unactivated Aryl Chlorides

Copper(I) Carbenes: The Synthesis of Active Intermediates in Copper-Catalyzed Cyclopropanation

Cyclic Dimers of Metalloporphyrins as Tunable Hosts for Fullerenes: A Remarkable Effect of Rhodium(III)

T. Nakajima, A. Ishiguro,
Y. Wakatsuki* ◆

V. Hagen,* J. Bendig, S. Frings,
T. Eckardt, S. Helm, D. Reuter,
U. B. Kaupp ◆

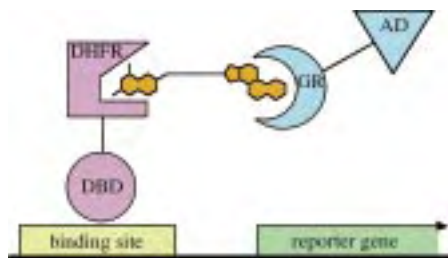
M. M. Olmstead,
A. de Bettencourt-Dias,
J. C. Duchamp, S. Stevenson,
D. Marciu, H. C. Dorn,*
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S. K. Das, J.-M. Mallet,
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J.-P. Hèrault, J.-M. Herbert,
M. Petitou,* P. Sinaÿ*
G. Y. Li*

B. F. Straub, P. Hofmann*

J.-Y. Zheng, K. Tashiro,
Y. Hirabayashi, K. Kinbara,
K. Saigo,* T. Aida,*
S. Sakamoto, K. Yamaguchi

The scope of cell-based assays is being expanded to allow the detection of interactions between proteins and DNA, RNA, or small molecules. The yeast two-hybrid assay, which normally detects protein–protein interactions, can be modified to detect interactions between ligands (the two dark yellow shapes in the diagram) and receptors (DHFR or GR). A small bridging molecule (made up of the ligands joined together) is used to join two fusion proteins (DHFR–DBD and AD–GR), thereby activating the reporter gene.



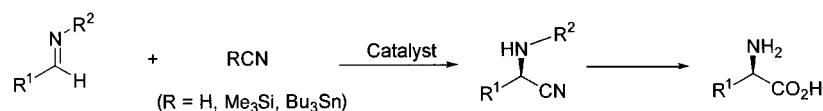
Angew. Chem. **2001**, *113*, 895–899

H. Lin, V. W. Cornish* 871–875

In Vivo Protein–Protein Interaction Assays: Beyond Proteins

Keywords: dimerization • molecular recognition • proteins • protein–protein interactions

150 years after its discovery, a truly efficient three-component asymmetric version of the Strecker reaction has finally been accomplished; there has also been significant progress in recent years in two-component Strecker-type systems: Enantiopure amino acids can now be obtained from enantioselective catalysis of the Strecker reaction with different cyanide sources and aldimines (see scheme).



Angew. Chem. **2001**, *113*, 900–902

L. Yet* 875–877

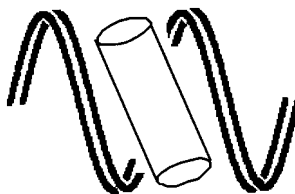
Recent Developments in Catalytic Asymmetric Strecker-Type Reactions

Keywords: amino acids • asymmetric catalysis • cyanides • Schiff bases • Strecker reaction

COMMUNICATIONS



In the groove! A tetracationic supramolecular cylinder, $[\text{Fe}_2\text{L}_3]^{4+}$ ($\text{L} = \text{C}_{25}\text{H}_{20}\text{N}_4$), with a triple-helical architecture is just the right size to fit into the major groove of DNA (see picture) and too big to fit into the minor groove. NMR spectroscopic data confirm that the cylinder binds in the major groove. Linear dichroism shows that very low loadings of $[\text{Fe}_2\text{L}_3]^{4+}$ have a dramatic bending effect on the DNA and atomic force microscopy images show that this is an intramolecular effect resulting in coils of DNA.



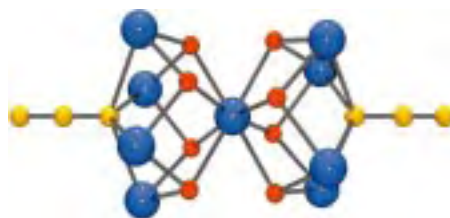
Angew. Chem. **2001**, *113*, 904–908

M. J. Hannon,* V. Moreno,* M. J. Prieto, E. Moldrheim, E. Sletten,* I. Meistermann, C. J. Isaac, K. J. Sanders, A. Rodger* 880–884

Intramolecular DNA Coiling Mediated by a Metallo-Supramolecular Cylinder

Keywords: bioinorganic chemistry • DNA recognition • DNA structures • helical structures • supramolecular chemistry

μ_4 end-on coordination (through the N atom) of the pseudohalogeno ligands $\text{X}^- = \text{N}_3^-$ and NCO^- has been observed in the isostructural nonanuclear Co^{II} cages with the general formula $[\text{Co}_9\{(2\text{-C}_5\text{H}_4\text{N})_2\text{-CO}_2\}_4(\text{O}_2\text{CMe})_8\text{X}_2]$ (see picture); this mode is imposed by the trapping of anions X^- into cavities formed inside the cage. The change of X^- modulates the magnetic behavior of the cage from antiferromagnetic coupling to a ferrimagnetic high-spin ground state.



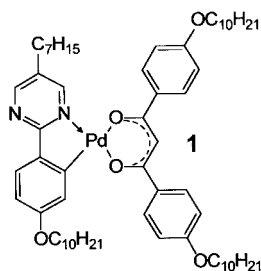
Angew. Chem. **2001**, *113*, 908–910

G. S. Papaefstathiou, S. P. Perlepes, A. Escuer,* R. Vicente, M. Font-Bardia, X. Solans 884–886

Unique Single-Atom Binding of Pseudohalogeno Ligands to Four Metal Ions Induced by Their Trapping into High-Nuclearity Cages

Keywords: azides • cage compounds • cobalt • high-spin molecules • magnetic properties

Molecular self-organization, driven by attractive face-to-face interactions between **1** and 2,4,7-trinitrofluorenone, leads to the formation of an optically biaxial smectic A liquid crystalline phase—a long-predicted new state of ordered soft matter.



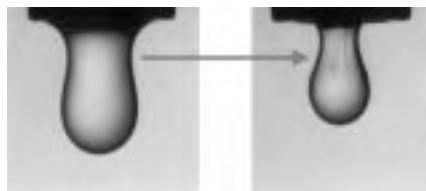
T. Hegmann, J. Kain, S. Diele, G. Pelzl, C. Tschierske* 887–890

Evidence for the Existence of the McMillan Phase in a Binary System of a Metallomesogen and 2,4,7-Trinitrofluorenone

Keywords: donor–acceptor systems • liquid crystals • mesophases • metallomesogens • palladium

Angew. Chem. **2001**, *113*, 911–914

Folded drops: A skinlike folded drop surface is formed by the coadsorption of two components from different phases at the chloroform/water interface (see picture). Both pure β -lactoglobulin and mixtures of α -dipalmitoylphosphatidylcholine (DPPC) and β -lactoglobulin can form the skinlike film; the lipid accelerates this process by coadsorption with the protein. Atomic force microscopy provided information on the morphology of the complex film and confirmed the formation of a multilayer film at the liquid/liquid interface.



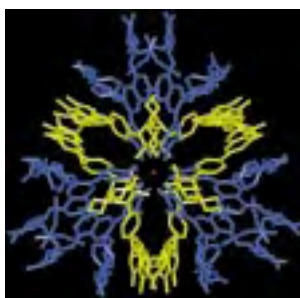
J. B. Li,* Y. Zhang, L. L. Yan .. 891–894

Multilayer Formation on a Curved Drop Surface

Keywords: atomic force microscopy • emulsions • multilayers • phospholipids • proteins • surface chemistry

Angew. Chem. **2001**, *113*, 915–918

The chirality of the sugar moiety is responsible for the chiral molecular recognition on formation of a metalloanthocyanin from *Salvia patens*. This mechanism was revealed by using the synthetic apigenin 7,4'-diglucosides derived from D- or L-glucose. The supermolecule (see picture) consists of six malonylwobanin molecules (blue) coordinated to two Mg^{2+} ions (red) with an *M*-helical arrangement of six 7,4'-diglucoside molecules (yellow) intercalated.



T. Kondo,* K.-i. Oyama, K. Yoshida 894–897

Chiral Molecular Recognition on Formation of a Metalloanthocyanin: A Supramolecular Metal Complex Pigment from Blue Flowers of *Salvia patens*

Keywords: chirality • glycosylation • metalloanthocyanins • molecular recognition • natural products

Angew. Chem. **2001**, *113*, 918–922

Comprehensive structure–function analyses are possible with an array comprising more than 800 synthetic variants of a protein domain composed of 44 amino acids. This array was produced by SPOT synthesis on a cellulose membrane (see schematic representation) and successfully employed for a parallel ligand-binding assay.



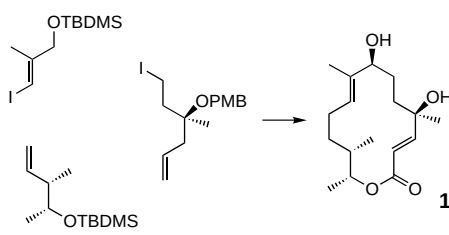
F. Toepert,* J. R. Pires, C. Landgraf, H. Oschkinat, J. Schneider-Mergener* 897–900

Synthesis of an Array Comprising 837 Variants of the hYAP WW Protein Domain

Keywords: peptides • peptide synthesis • proteins • solid-phase synthesis

Angew. Chem. **2001**, *113*, 922–925

Three building blocks are coupled convergently in the first total synthesis of the macrolide antibiotic 5,6-tetrahydrocineromycin B (**1**); the facial selective allylation of a methyl ketone is the key step of the synthesis. TBDMS = *tert*-butyldimethylsilyl, PMB = *p*-methoxybenzyl.



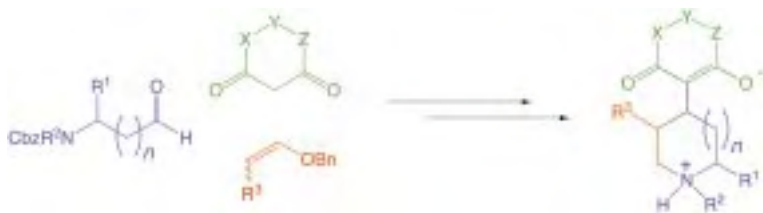
L. F. Tietze,* L. Völkel 901–902

Total Synthesis of the Macrolide Antibiotic 5,6-Dihydrocineromycin B

Keywords: allylation • antibiotics • lactones • macrolides • total synthesis

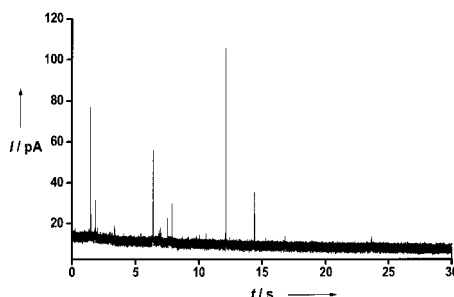
Angew. Chem. **2001**, *113*, 925–927

Advantages of solid-phase and liquid-phase synthesis are combined in a new concept of combinatorial chemistry: a domino sequence comprising Knoevenagel and hetero-Diels–Alder reactions with subsequent hydrogenation starting from protected aminoaldehydes, 1,3-dicarbonyl compounds, and enol ethers leads to N-heterocycles of high diversity with a betaine structure, which are isolated in highly pure form by precipitation with diethyl ether (see scheme). Cbz = benzyloxycarbonyl, Bn = benzyl.



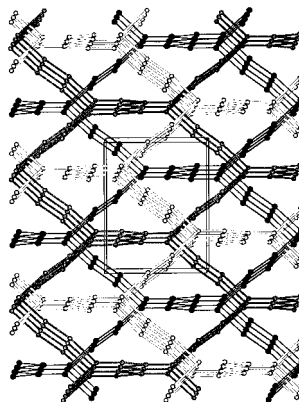
Angew. Chem. **2001**, *113*, 927–929

Positioning a carbon-fiber microelectrode with optimized stiffness and vibration characteristics in close proximity to an individual biological cell is achieved by using a shear-force-based constant-distance control in the scanning electrochemical microscope. With the properly positioned microelectrode, the discrete release of neurotransmitters from individual cells can be monitored (see diagram; I = oxidation current).



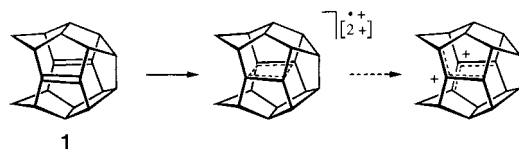
Angew. Chem. **2001**, *113*, 942–946

Inseparably interwoven are three independent polymeric diamond-type $U(P_2S_6)_2$ frameworks in the structure of the title compound (see picture). The linear P_2S_6 units act as molecular rods linking the pseudotetrahedral U^{4+} centers. $U(P_2S_6)_2$ may be viewed as a coordination polymer which is formed from U/P/S melts by the solid-state equivalent of the self-assembly reactions in solution.



Angew. Chem. **2001**, *113*, 946–948

For the seco-dodecahedradiene 1, in which the distance $d_{\pi\pi}$ between the carbon atoms of the two double bonds ranges from 2.90 to 3.20 Å and pyramidalization angles Φ range from 14.9 to 35.5°, the geometrical prerequisites for in-plane (σ)-homoconjugative (σ -bishomoaromatic) electron delocalization in $4C/3(2)e$ cations could be better defined. Whilst the $4C/3e$ radical cation is persistent in a matrix, the $4C/2e$ dication in superacid medium is, at best, an intermediate en route to the stable bisallylic dication.



Angew. Chem. **2001**, *113*, 930–933

L. F. Tietze,* H. Evers,
E. Töpken 903–905

A Novel Concept in Combinatorial Chemistry in Solution with the Advantages of Solid-Phase Synthesis: Formation of N-Betaines by Multicomponent Domino Reactions

Keywords: amino aldehydes • betaines • combinatorial chemistry • domino reactions • multicomponent reactions

A. Hengstenberg, A. Blöchl, I. D. Dietzel,
W. Schuhmann* 905–908

Spatially Resolved Detection of Neurotransmitter Secretion from Individual Cells by Means of Scanning Electrochemical Microscopy

Keywords: electrochemistry • exocytosis • microelectrodes • neurotransmitters • scanning probe microscopy

C. Gieck, F. Rocker, V. Ksenofontov,
P. Gütllich, W. Tremel* 908–911

“Supramolecular” Solid-State Chemistry: Interpenetrating Diamond-Type Frameworks of U^{4+} Ions Linked by S,S' -Bidentate $P_2S_6^{2-}$ Molecular Rods in UP_4S_{12}

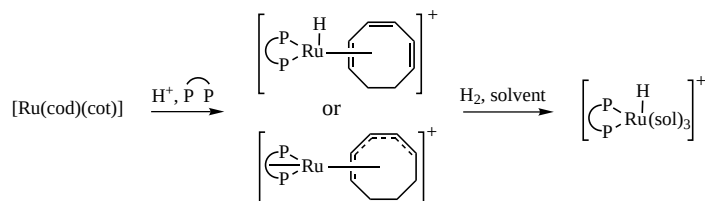
Keywords: chalcogenides • networks • solid-state structures • supramolecular chemistry • uranium

H. Prinzbach,* J. Reinbold, M. Bertau,
T. Voss, H.-D. Martin, B. Mayer,
J. Heinze, D. Neschchadin, G. Gescheidt,
G. K. S. Prakash, G. A. Olah .. 911–914

σ -Bishomoconjugation (σ -Bishomoaromaticity) in $4C/3(2)e$ Cations—Scope and Limitations

Keywords: aromaticity • cage compounds • cyclic voltammetry • photoelectron spectroscopy • superacidic systems

Simple and efficient: Protonation of $[\text{Ru}(1,2:5,6-\eta\text{-cod})(\eta^6\text{-cot})]$ ($\text{cod} = 1,5\text{-cyclo-octadiene}$, $\text{cot} = 1,3,5\text{-cyclooctatriene}$) with $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ and then reaction with chiral bisphosphane ligands ($\text{P} \cdot \text{P} = \text{Me-DuPHOS}$, BINAP, Tol-BINAP, JOSIPHOS) affords the corresponding $[\text{Ru}(\text{P} \cdot \text{P})(\text{H})(\eta^6\text{-cot})]^+$ or $[\text{Ru}(\text{P} \cdot \text{P})(1,2,3,4,5-\eta\text{-C}_8\text{H}_{11}')^+]$ ($\text{C}_8\text{H}_{11}' = 2,4\text{-cyclooctadienyl}$; see scheme). Exposure of these cations to H_2 in solvents (sol) such as acetone, methanol, and THF affords $[\text{Ru}(\text{P} \cdot \text{P})(\text{H})(\text{sol})_3]^+$, which are catalysts for (amongst other things) enantioselective hydrogenations of alkenes.



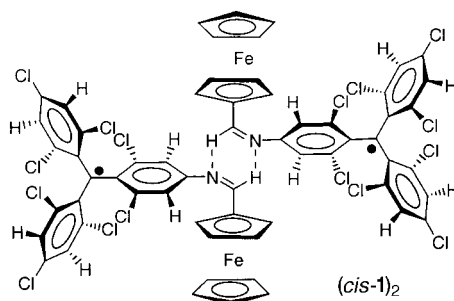
Angew. Chem. **2001**, *113*, 937–942

J. A. Wiles, S. H. Bergens,*
K. P. M. Vanhessche, D. A. Dobbs,
V. Rautenstrauch* 914–919

A Versatile and High-Yield Route to
Active and Well-Defined Catalysts
 $[\text{Ru}(\text{bisphosphane})(\text{H})(\text{solvent})_3](\text{BF}_4)$

Keywords: asymmetric catalysis •
homogeneous catalysis •
hydrogenation • P ligands • ruthenium

An irreversible *trans* → *cis* isomerization of the imino group occurs during the irradiation of the new ferrocenyl Schiff-base polychlorotriphenylmethyl radical **1** by light. Low-temperature ESR investigations of frozen solutions revealed that the *cis* isomer exists as the (*cis*-**1**)₂ dimer with strong antiferromagnetic interactions. The radical **1** constitutes an example of a one-way photoswitchable magnetic system in which a conversion between a doublet and a singlet ground-state species is promoted by a photoinduced self-assembly process driven by the formation of hydrogen bonds.



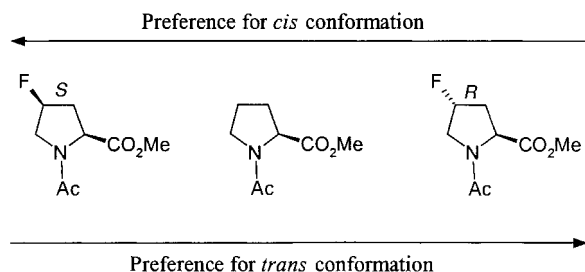
I. Ratera, D. Ruiz-Molina,
J. Vidal-Gancedo, K. Wurst, N. Daro,
J.-F. Létard, C. Rovira,
J. Veciana* 919–922

A New Photomagnetic Molecular System
Based on Photoinduced Self-Assembly of
Radicals

Keywords: isomerization •
magnetic properties • photochemistry •
radicals • self-assembly

Angew. Chem. **2001**, *113*, 933–936

The preference of the peptidyl–fluoroproline amide bond for the *cis* or *trans* conformation in the model compounds *N*-acetyl-4-fluoroproline methyl esters (see scheme) fully correlates with the thermostability of the related mutants of the model protein barstar. Thus, the (4*S*)-L-FPro mutants show a higher and the (4*R*)-L-FPro mutants a lower thermal stability than barstar.



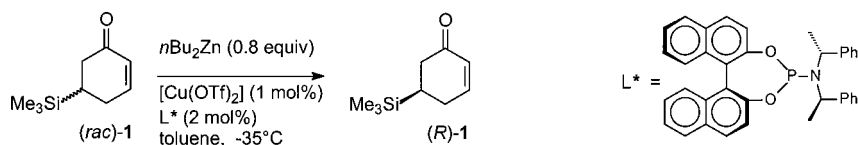
Angew. Chem. **2001**, *113*, 949–951

C. Renner, S. Alefelder, J. H. Bae,
N. Budisa, R. Huber,
L. Moroder* 923–925

Fluoroprolines as Tools for Protein
Design and Engineering

Keywords: fluorine • isomerization •
NMR spectroscopy • proline • proteins

A variety of substituted 2-cyclohexenones, such as (*R*)-**1**, is obtained enantiomerically pure by employing the chiral copper–phosphoramidite complex [Cu(OTf)₂L*] as a highly efficient catalyst for their kinetic resolution (> 99% *ee* at 52% conversion, selectivity *S* > 200). These important building blocks can be obtained on a synthetically interesting scale, as was demonstrated by the successful multigram resolution of 5-methyl-2-cyclohexenone. Tf = trifluoromethanesulfonyl.



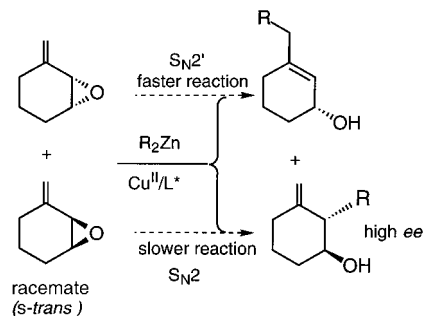
Angew. Chem. **2001**, *113*, 953–956

R. Naasz, L. A. Arnold, A. J. Minnaard, B. L. Feringa* 927–930

Highly Enantioselective Copper–Phosphoramidite Catalyzed Kinetic Resolution of Chiral 2-Cyclohexenones

Keywords: asymmetric catalysis • copper • enones • kinetic resolution • phosphoramidites

Chiral recognition leads to enantio- and regiodivergent reactivity: An unusual regiodivergent catalytic kinetic resolution has been accomplished for the first time in an organometallic reaction in which a C–C bond is formed. Chiral copper complexes of the non-racemic phosphoramidite ligand L* discriminate the enantiomers of semirigid vinyl-oxiranes (having a blocked *s-cis* or *s-trans* conformation) to give separable regioisomeric products with very high stereocontrol in a two-step process (see scheme).



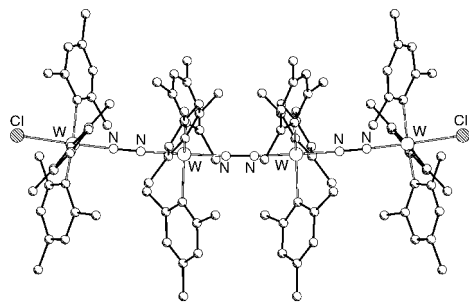
Angew. Chem. **2001**, *113*, 956–958

F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi,* B. L. Feringa* .. 930–932

Highly Enantioselective Regiodivergent and Catalytic Parallel Kinetic Resolution

Keywords: asymmetric catalysis • copper • elimination • kinetic resolution • phosphoramidites

A new avenue is opened up in the potential use of dinitrogen. Oligomerization of the metalla–dinitrogen functionality leads to the formation of polymers based on a [–(Mes)₃W–N₂–]_{*n*} moiety (see picture).



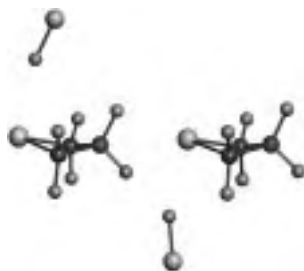
Angew. Chem. **2001**, *113*, 958–960

E. Solari, J. Hesschenbrouck, R. Scopelliti, C. Floriani,* N. Re 932–934

From Oligomers to Conducting Polymers of the Metal–Dinitrogen Functionality

Keywords: dinitrogen • metallacycles • oligomers • tungsten

Two different conformers (axial (in the left picture) and equatorial (right)) are formed in a supersonic jet stream when trimethylene sulfide, a floppy molecule with a large-amplitude ring-puckering motion, is complexed to hydrogen chloride. The axial conformer is the most stable. The relaxation from the equatorial to the axial conformational has been observed using different carrier gases.



Angew. Chem. **2001**, *113*, 961–964

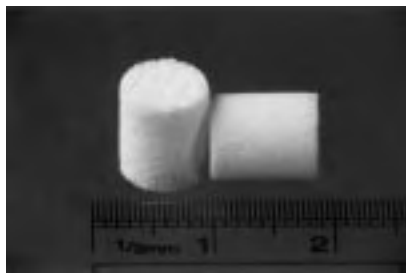
M. E. Sanz, A. Lesarri, J. C. López, J. L. Alonso* 935–938

Hydrogen Bond in Molecules with Large-Amplitude Motions: A Rotational Study of Trimethylene Sulfide···HCl

Keywords: conformational analysis • hydrogen bonds • large-amplitude motions • rotational spectroscopy

A new resin support generated by co-sintering resin beads with an inert polymer (see picture) facilitates resin handling. A wide range of reactions was carried out to demonstrate its applicability and its comparability to the free resin.

Angew. Chem. **2001**, *113*, 964–967



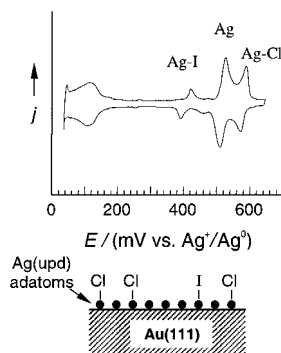
B. Atrash, M. Bradley,* R. Kobylecki,*
D. Cowell, J. Reader 938–941

Revolutionizing Resin Handling for
Combinatorial Synthesis

Keywords: combinatorial chemistry •
polymer supports • synthetic methods

A new strategy for detecting halides is presented that employs gold electrodes plated to expose a monolayer of silver atoms. Cl^- , Br^- , and I^- ions each adsorb onto this surface and stochastically produce electrochemical changes (see picture; upd = underpotentially deposited) in the stripping characteristic of the silver layer that reflect the identity and surface coverage of these halides. The latter provides measurements that relate to the solution concentrations of the halides.

Angew. Chem. **2001**, *113*, 967–970

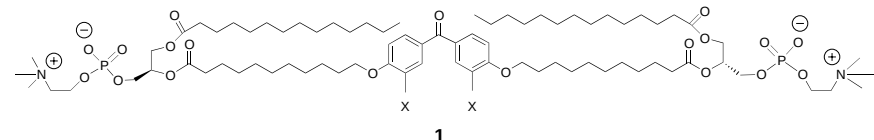


R. Michalitsch, P. E. Laibinis* . 941–944

Adsorption-Mediated Electrochemical
Sensing of Halides

Keywords: cyclic voltammetry •
electrochemistry • halides • sensors •
silver

The tandem use of the photosensitive bola-amphiphile 1 ($\text{X} = {}^3\text{H}$) and cholesterol enabled the determination of the center of the transmembrane domain of glycoprotein A (131 amino acid residues) in a membrane by selective functionalization of the protein within a phospholipid bilayer.



Angew. Chem. **2001**, *113*, 970–972

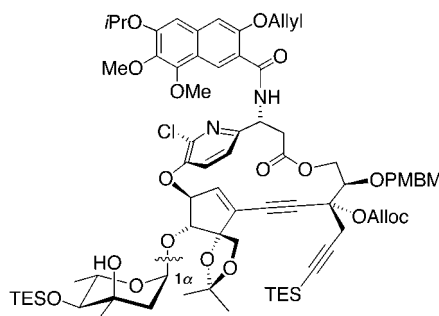
Y. Ogawa, W. Hahn, P. Garnier,
N. Higashi, D. Massotte,
M.-H. Metz-Boutigue, B. Rousseau,
J. Sunamoto, G. Ourisson,
Y. Nakatani* 944–946

Mid-Membrane Photolabeling of the
Transmembrane Domain of
Glycoprotein A in Phospholipid Vesicles

Keywords: cross-coupling • liposomes •
membrane proteins • photolabeling •
protein structures

The α -selective effect and potency of AgPF_6 on readily prepared 2-deoxythioglycosides allows the direct attachment of a partially protected *allo*-sugar, such as L-mycarose, to an advanced and hindered aglycon unit of kedarcidin (see picture). This method also permits access to other 2-deoxyglycosides in an expedient and mild manner. PMBM = *p*-methoxybenzyloxy-methyl, Alloc = allyloxycarbonyl, TES = triethylsilyl.

Angew. Chem. **2001**, *113*, 972–975

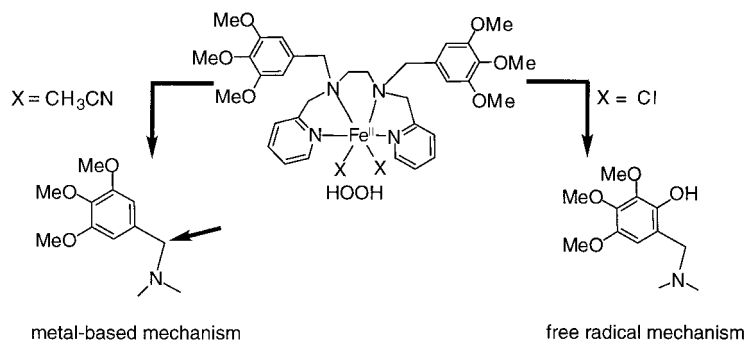


M. J. Lear, F. Yoshimura,
M. Hiramata* 946–949

A Direct and Efficient α -Selective
Glycosylation Protocol for the Kedarcidin
Sugar, L-Mycarose: AgPF_6 as a
Remarkable Activator of
2-Deoxythioglycosides

Keywords: deoxy sugars •
glycosylation • kedarcidin •
silver hexafluorophosphate •
stereoselectivity

Manipulation of the coordination sphere of an Fe^{II} ion can be used to tune the balance between different catalytic pathways for oxidation (OH[•] versus iron-based oxidant; see scheme). This reinvestigation of Fenton chemistry uses the iron complex shown as a mechanistic probe.



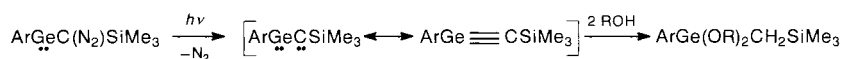
Angew. Chem. **2001**, *113*, 975–978

Y. Mekmouche, S. Ménage,*
C. Toia-Duboc, M. Fontecave,
J.-B. Galey, C. Lebrun,
J. Pécaut 949–952

H₂O₂-Dependent Fe-Catalyzed
Oxidations: Control of the Active Species

Keywords: homogeneous catalysis •
hydrogen peroxide • hydroxylation •
iron • reaction mechanisms

Photolysis of a diazogermylene generates a germylene–carbene species, a resonance form of a germyne (see scheme). Support for the intermediacy of the triply bonded form in the trapping reaction with an alcohol is provided by the fact that the diazo precursor does not behave as a germylene and that its photolysis product does not react with carbene traps such as 2,3-dimethylbutadiene. Hence, this is the first chemical evidence for a germyne. Ar = 2,6-(*i*Pr₂NCH₂)₂C₆H₃; R = Me, *t*Bu.



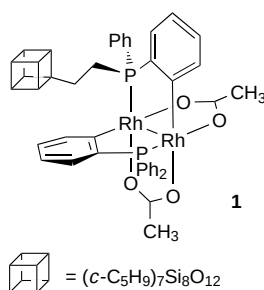
Angew. Chem. **2001**, *113*, 978–980

C. Bibal, S. Mazières, H. Gornitzka,
C. Couret* 952–954

A Route to a Germanium–Carbon Triple
Bond: First Chemical Evidence for a
Germyne

Keywords: carbenes •
diazo compounds • germanium •
multiple bonds • photolysis

Supported, air stable, and reusable hydroformylation catalysts have been prepared by immobilizing dinuclear rhodium(II) complexes bearing *ortho*-metalated arylphosphane ligands on amorphous silica and mesoporous MCM-41 supports by phosphane tethers. The oligosilsesquioxane model complex of the catalytic site **1** has been prepared analogously and characterized by single-crystal X-ray diffraction analysis.



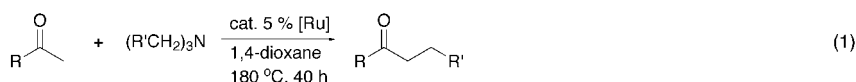
Angew. Chem. **2001**, *113*, 981–984

M. Nowotny,* T. Maschmeyer,*
B. F. G. Johnson, P. Lahuerta,
J. M. Thomas, J. E. Davies 955–958

Heterogeneous Dinuclear Rhodium(II)
Hydroformylation Catalysts—
Performance Evaluation and
Silsesquioxane-Based Chemical Modeling

Keywords: heterogeneous catalysis •
hydroformylation • immobilization •
mesoporosity • rhodium

A new reaction: A ruthenium-catalyzed transfer of an alkyl group from a trialkylamine to the α -carbon atom of a ketone leads in good yields to α -alkylated ketones [Eq. (1)]. The reaction is applicable to a wide range of alkyl(alkyl), alkyl(aryl), and cyclic ketones, and in the case of unsymmetrical ketones it takes place regioselectively at the less hindered α -position.



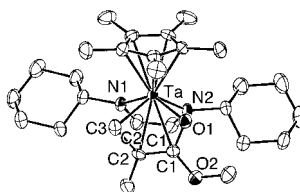
Angew. Chem. **2001**, *113*, 984–986

C. S. Cho,* B. T. Kim, M. J. Lee,
T.-J. Kim, S. C. Shim* 958–960

Ruthenium-Catalyzed Regioselective
 α -Alkylation of Ketones: The First Alkyl-
Group Transfer from Trialkylamines to
the α -C Atom of Ketones

Keywords: alkylation • amines •
homogeneous catalysis • ketones •
ruthenium

Activation with AlMe_3 at low temperature converts half-metallocene complexes of tantalum with methyl methacrylate (MMA) and diazadiene ligands such as $[\text{Cp}^*\text{Ta}(\eta^2\text{-Cy-DAD})(\eta^4\text{-MMA})]$ (structure shown) into effective catalysts for the polymerization of MMA. Polymerization is complete after 10 min at -20°C and gives a poly-(methyl methacrylate) of narrow polydispersity. $\text{Cp}^* = \eta^5\text{-C}_5\text{H}_5$, Cy-DAD = 1,4-dicyclohexyl-1,4-diaza-1,3-butadiene.



Y. Matsuo, K. Mashima,*
K. Tani 960–962

Half-Metallocene Tantalum Complexes Bearing Methyl Methacrylate (MMA) and 1,4-Diaza-1,3-diene Ligands as MMA Polymerization Catalysts

Keywords: diazadienes • homogeneous catalysis • metallocenes • polymerization • tantalum

Angew. Chem. **2001**, *113*, 986–988



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* Author to whom correspondence should be addressed



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Automated Synthetic Methods for Speciality Chemicals W. Hoyle *H.-U. Blaser, M. Studer* 964



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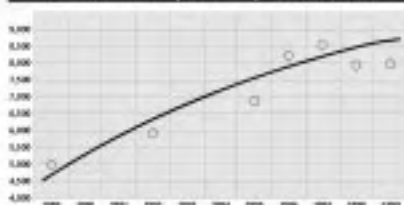
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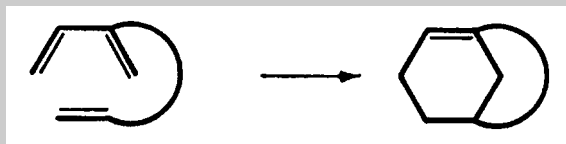
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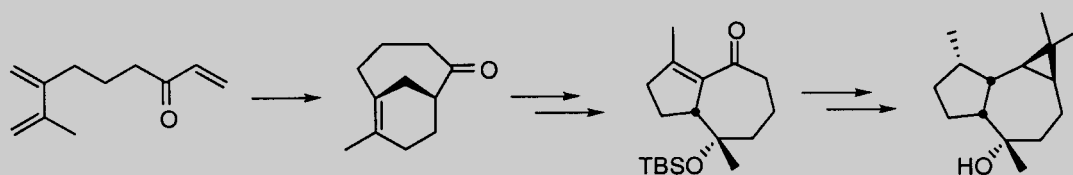
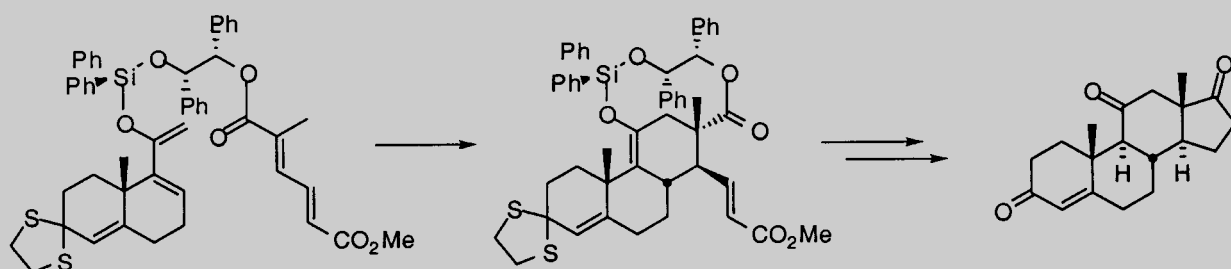
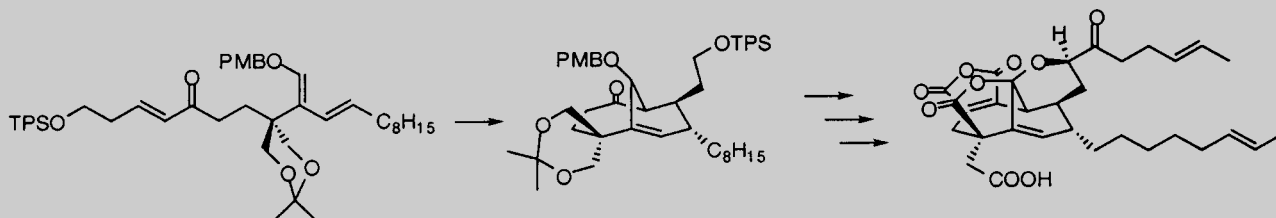
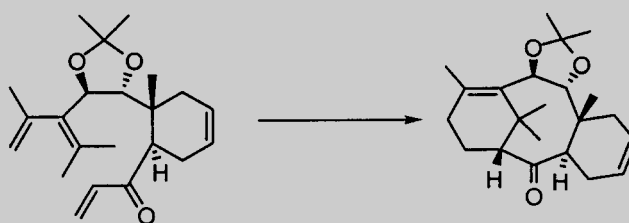
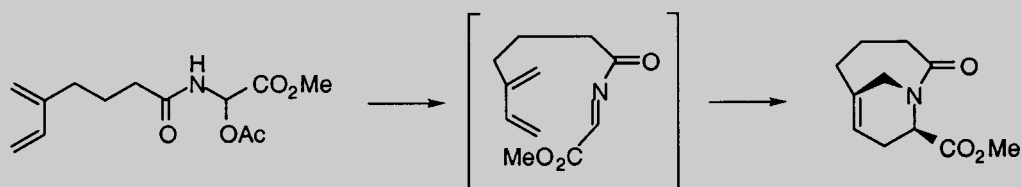


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The Type 2 Intramolecular Diels–Alder Reaction



a Versatile Synthetic Tool



The Type 2 Intramolecular Diels–Alder Reaction: Synthesis and Chemistry of Bridgehead Alkenes

Brian R. Bear, Steven M. Sparks, and Kenneth J. Shea*

Anti-Bredt alkenes, bicyclic molecules that contain a bridgehead double bond, were for many years regarded as chemical curiosities. The type 2 intramolecular Diels–Alder (IMDA) reaction provides a one-step entry into this fascinating class of molecules. The reaction has made available numerous anti-Bredt alkenes for structural and chemical studies. X-ray crystallography has revealed the magnitude of the deformations associated with the bridgehead double bond, and rate

studies of reactions of bridgehead alkenes have allowed quantification of the kinetic consequences of the torsional distortions. More recently, the type 2 intramolecular Diels–Alder reaction and the resulting anti-Bredt alkenes have found application in organic synthesis. The constraints resulting from the connectivity in the Diels–Alder precursor creates a strong regio- and stereochemical bias in the cycloaddition step. The end result of this bias is the stereoselective synthesis of

highly substituted six-membered rings. The reaction also achieves a facile synthesis of seven- and eight-membered rings in a single step from acyclic precursors. The utility of this reaction has been verified in recent applications of the type 2 IMDA reaction as a key step in the total synthesis of complex natural products.

Keywords: bridgehead alkenes • natural products • strained molecules • synthetic methods

1. Introduction

There are two types of connectivity available to the intramolecular variant of the Diels–Alder reaction. When diene and dienophile are joined at position 1 of the diene (type 1), cycloaddition usually gives rise to a fused bicyclic adduct [Eq. (1)]. This reaction has assumed considerable



importance in contemporary organic synthesis.^[1] A second variant involves union of diene and dienophile at position 2 of the diene (type 2). Cycloaddition in this case results in formation of a bridged bicyclic ring system [Eq. (2)]. The reaction has substantial synthetic potential since there are few methods that yield a bridged bicyclic structure in a single step



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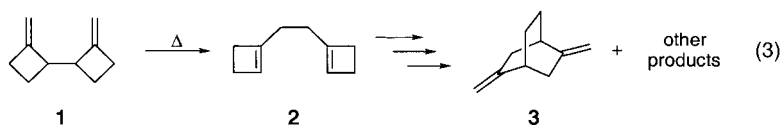
from an acyclic precursor. The product of the type 2 intramolecular Diels–Alder (type 2 IMDA) cycloaddition contains a bridgehead double bond, it is an anti-Bredt alkene. Thus, the reaction provides a direct entry into this interesting class of molecules.^[2]

We describe herein events leading to the discovery of the type 2 IMDA cycloaddition, as well as a summary of the scope of the reaction and an evaluation of its synthetic utility. The reaction has been used for synthesis of both strained and unstrained bridgehead alkenes. The availability of bridgehead alkenes has provided opportunities to study both their structure and reactivity. As the extent of the reaction unfolded, type 2 intramolecularity has found increasing importance in synthetic methodology as a general strategy for controlling both stereochemistry and regiochemistry of the Diels–Alder reaction. More recently, there has been a growing number of applications of this reaction in the synthesis of natural products. A survey of these applications is included in the final section of the review.

2. Background

The first report of a type 2 IMDA cycloaddition appeared in 1978.^[3] The reaction was discovered serendipitously during a mechanistic study of the Cope rearrangement.^[4, 5] The [3,3]

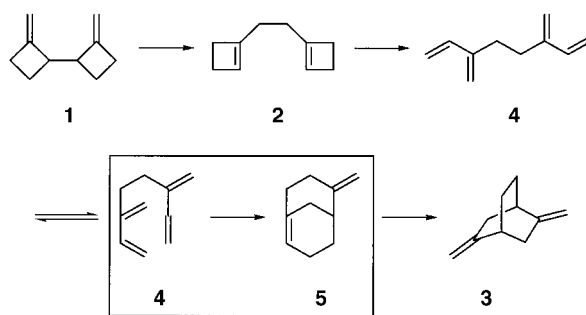
sigmatropic rearrangement of the *d,l*- and *meso*-bismethylene cycloalkanes was investigated as a method to independently probe the chair and boat transition states of the Cope rearrangement. As part of the study, the thermolysis of bis(methylenecyclobutane) **1** was undertaken [Eq. (3)]. The



reaction was unexpectedly complex, ultimately leading to no less than seven isomeric products. The anticipated Cope product **2** was not detected from the thermolysis of **1** at high temperatures (flow pyrolysis, $T \geq 300^\circ\text{C}$, 10 s). From this complex reaction mixture, one of the more interesting compounds was 2,5-bismethylenebicyclo[2.2.2]octane (**3**).

The connectivity of **3** presented the investigators with a mechanistic conundrum. Following its independent synthesis to verify the proposed structure, a tentative explanation was forwarded. The proposal involved the cascade of reactions outlined in Scheme 1. Bis(methylenecyclobutane) (**1**) was thought to undergo an initial [3,3] sigmatropic rearrangement to produce **2**. At high temperatures ($\geq 300^\circ\text{C}$) sequential electrocyclic ring opening of both cyclobutenes followed to afford intermediate tetraene **4**.^[6] At this point, the connectivity in the final product **3** strongly implied a two-step

sequence initiated by an intramolecular Diels–Alder reaction (type 2!) which would give rise to the highly strained anti-Bredt alkene **5**. A *formal* [3,3] sigmatropic rearrangement remained to complete the transformation to **3**, a local thermodynamic sink. What was troubling at the time was the seemingly improbable and unprecedented Diels–Alder step in this cascade of reactions. Notwithstanding, careful reexamination of the thermolysis reaction mixture provided support for the proposal. Guided initially by olfactory clues,^[7] small quantities of bridgehead alkene **5** were isolated from reaction mixtures by preparative GC. Despite limited quantities of this reactive molecule, it was possible to acquire adequate spectroscopic data for characterization. It was also established that when the reactive bridgehead alkene **5** was subjected to the gas-phase



Scheme 1. Proposed reaction cascade leading to **3**.

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B. R. Bear



S. M. Sparks



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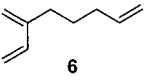
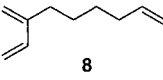
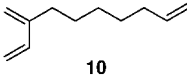
Steven M. Sparks was born in 1972 and grew up in Stockbridge, Massachusetts. He received his BS degree from Rensselaer Polytechnic Institute in 1995, during which he completed a research internship at Burroughs Wellcome in the division of Organic Chemistry. Following a year as a research technician at Albany Molecular Research, he began graduate studies at the University of California, Irvine under the direction of Professor Kenneth J. Shea. His research interests include development of hetero type 2 Diels–Alder methodology and natural product synthesis.

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thermolysis conditions it underwent rearrangement to **3**. The isolation and characterization of strained bridgehead alkene **5** provided the first evidence that type 2 connectivity was compatible with the Diels–Alder cycloaddition despite the fact that the product of the reaction was a strained anti-Bredt alkene. These findings not only resolved a mechanistic puzzle, but presented an opportunity to consider the generality of the reaction.

The first step in this evaluation involved an investigation of the thermal behavior of a series of acyclic trienes (Table 1).^[3] These homologous trienes were found to undergo type 2

Table 1. Type 2 IMDA cycloadditions of acyclic trienes.

Starting material	Conditions	Product	Conversion [%]
 6	420 °C, 23 s	 7	32
 8	455 °C, 5 s	 9	55
 10	510 °C, 8 s	 11	29

IMDA reaction under conditions similar to those used for the thermolysis of **1** (400–500 °C, gas phase, atmospheric pressure, ca. 10–15 s contact time). The products of the reaction, the corresponding carbocyclic bridgehead alkenes, were produced as single regioisomers. Of special note was the formation of the prototypical anti-Bredt alkene, bicyclo[3.3.1]nonene (**7**), a molecule first prepared in 1967 by Marshall and Faubl^[8] as well as Wiseman^[9] by elimination of the corresponding bridgehead-substituted bicyclic precursor. Interestingly, under the high temperatures of the thermolysis conditions, triene **6** and bicyclo[3.3.1]nonene (**7**) exist in equilibrium (30:70 at 350 °C). The cycloadducts in Table 1 include products that contain seven- and eight-membered rings, a feature of this reaction that was later found to have considerable synthetic importance.

In the examples in Table 1, high temperatures were necessary to achieve cycloaddition. The high activation energy arises in part from the unactivated dienophiles in the Diels–Alder precursors and the strain in the bridgehead alkene product.^[10] Despite these high temperatures, atmospheric pressure flow thermolysis is amenable to large-scale preparation of simple bridgehead alkenes. The products can be separated by distillation to afford pure cycloadduct. These initial findings established that type 2 connectivity can be used for the synthesis of bridgehead alkenes.

Bridgehead alkenes incorporate a *trans*-cycloalkene substructure. The cycloadducts from the type 2 IMDA reaction possess the bicyclo[*n*.3.1] skeleton. The strain associated with the bridgehead double bond is related to the size of the

variable (*n*) bridge. For *n* = 3, that is bicyclo[3.3.1]nonene (**7**), the molecule contains a *trans*-cyclooctene ring and is the smallest, isolatable bridgehead alkene.^[2] The bridgehead double bond has been found to be 10⁶ times more reactive towards electrophiles than a simple unstrained trisubstituted double bond. The strain and reactivity fall off rapidly as *n* increases to 4 (*trans*-cyclononene) or 5 (*trans*-cyclodecene). Bridgehead alkenes incorporating the *trans*-cyclononene have been found to be 10³ times more reactive towards electrophiles than unstrained alkenes, while bicyclo[5.3.1]undecene derivatives are unstrained and exhibit similar reactivity to their nonbridged counterparts.

3. Development of the Scope of the Reaction

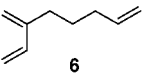
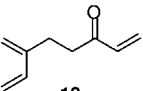
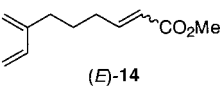
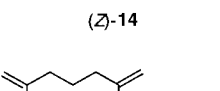
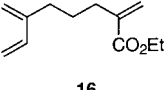
3.1. Synthesis of Substituted Derivatives of Bridgehead Alkenes

3.1.1. Activated Dienophiles

The introduction of activating substituents on the dienophile was found to moderate the conditions necessary for cycloaddition and importantly, provide synthetic entries into substituted derivatives of bridgehead alkenes.^[4, 11]

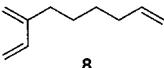
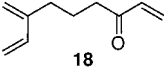
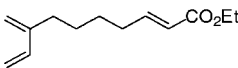
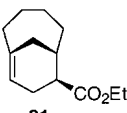
The cycloaddition of three- and four-atom bridged trienes (see Tables 2 and 3, respectively) reveal the influence of substituents on the reaction rate. In all cases, the reaction conditions were milder than those for the unactivated precursors. Enhanced activity was noted for activating groups both endocyclic and exocyclic to the tether joining diene and

Table 2. Gas-phase thermolysis of three-atom-bridged triene esters and ketones.

Starting material	Conditions ^[a]	Product	Yield [%] ^[b]
 6	420 °C, 23 s	 7	32
 12	395 °C, 18 s	 13	72
 (<i>E</i>)- 14	318 °C, 18 s	 15	76
 (<i>Z</i>)- 14	365 °C, 12 s	 15 ^[c]	
 16	390 °C, 12 s	 17	30

[a] Atmospheric pressure, N₂ carrier gas; thermolysis temperature and contact time are given. [b] Determined by GC, percentages based upon starting material remaining after thermolysis. [c] The *Z* isomer underwent isomerization to the *E* isomer under the thermolysis conditions. The cycloaddition product was identical with that obtained from (*E*)-**14**.

Table 3. Gas-phase thermolysis of four-atom-bridged triene esters and ketones.

Starting material	Conditions ^[a]	Product	Conversion [%] ^[b]
	455 °C, 8 s		55
	398 °C, 8 s		85
	420 °C, 8 s		80

[a, b] See Table 2.

dienophile. This later point is interesting since inspection of models of the transition state of the reaction of **12** reveals that it is not possible to achieve coplanarity of the carbonyl and alkene fragments of the dienophile.

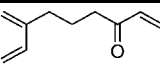
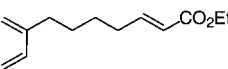
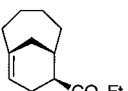
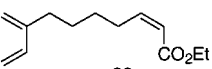
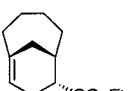
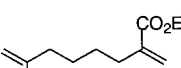
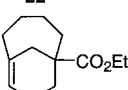
Subsequent investigations revealed that many of the cycloadditions could also be run in solution. Table 4 summarizes some of the first examples of these reactions. Cycloadditions are typically run in aromatic solvents in sealed tubes. Reaction temperatures ranged from 170 to 250 °C.

The preceding cycloadditions provide a one-step route to functionalized bridgehead alkenes from an acyclic precursor. In most cases the configuration of the dienophile is retained. The stereospecific formation of *endo*- and *exo*-bicyclic derivatives from the corresponding *cis*- and *trans*-alkenes, respectively, is consistent with a *concerted* cycloaddition (Table 4).

3.1.2. Lewis Acid Catalysis

Despite the high yields of the reactions given in Section 3.1.1, high temperatures were necessary to achieve cycloaddition. A later report described that many of the type 2 IMDA cycloadditions are amenable to Lewis acid catalysis. As with many reactions, the choice of catalyst is, in part at least, empirical. Table 5 summarizes the results of a study that uses diethylaluminum chloride for inducing the cycloaddition. These mild conditions (low

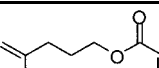
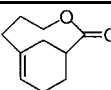
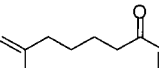
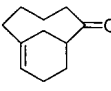
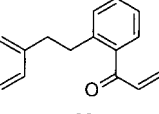
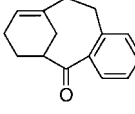
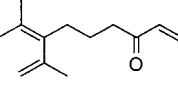
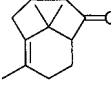
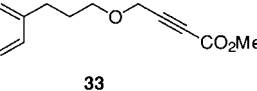
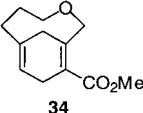
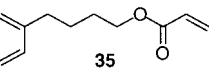
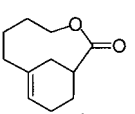
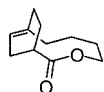
Table 4. Solution-phase thermolysis of triene esters and ketones.

Starting material	Conditions ^[a]	Product	Yield [%] ^[b]
	201 °C, 15 min		57
	206 °C, 2 h		80 ^[c] (91)
	232 °C, 4 h		65
	232 °C, 4 h		63

[a] Reactions were run in dilute (0.04–0.09 M) xylene solution. [b] Yields are calculated by GC referenced to an internal standard. [c] Yield of isolated product.

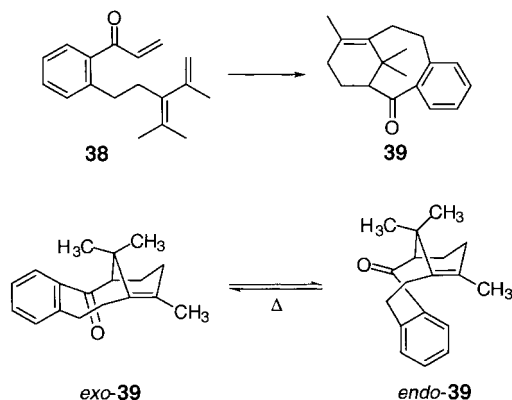
temperatures) and short reaction times are compatible with construction of more highly functionalized bridged bicyclic structures, further extending the synthetic utility of the reaction.^[12]

Table 5. Lewis acid catalyzed type 2 IMDA reactions.

Starting triene	Conditions ^[a]	Product	Yield [%]
	4 h, 21 °C		50
	2 h, 21 °C		75
	1 h, 21 °C		71
	< 5 min, 21 °C		70
	12 h, 21 °C		85
	1 h, 21 °C	 + 	90 (36:37 = 4:1)

[a] In CH₂Cl₂ with Et₂AlCl as Lewis acid; thermolysis temperature and reaction time are given.

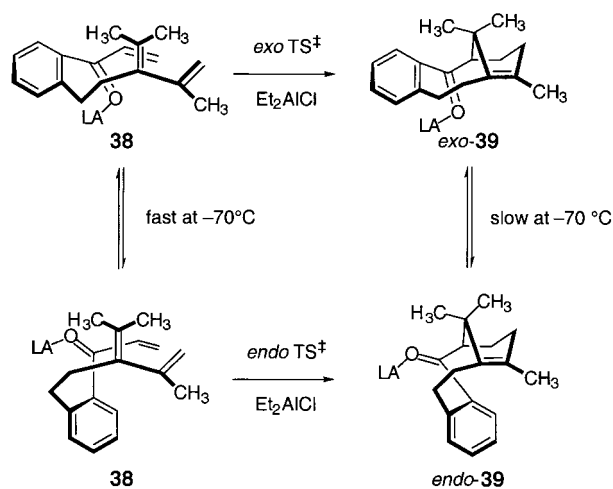
Lewis acid catalysis provided a unique opportunity to quantify the relative energies of two transition state conformers of the type 2 IMDA reaction of triene **38** (Scheme 2).^[13] Cycloadduct **39** exists as two conformers, *exo*-



Scheme 2. Cycloaddition of triene **38**.

39 and *endo*-**39**. The two conformational isomers are separated by an activation energy barrier of 16.5 kcal mol^{−1}. Under conditions of the thermal cycloaddition (155 °C, 93 h), the two conformers are rapidly equilibrated. At 25 °C, *endo*-**39** is the dominant conformational isomer (*endo*-**39**/*exo*-**39** = 89/11, $\Delta\Delta G^\circ = 1.24 \pm 0.15$ kcal mol^{−1}).

Alternatively, the reaction can be catalyzed by Et₂AlCl. At −70 °C, interconversion of the *endo* and *exo* conformational isomers of **38** is fast (Scheme 3). Interconversion of conforma-



Scheme 3. Competing reactions in the Lewis acid catalyzed cycloaddition of **38**.

tional isomers of **39**, however, is slow. Under Lewis acid catalysis the ratio *endo*-**39**/*exo*-**39** represents the kinetically controlled rate of product formation, $k_{\text{endo}}/k_{\text{exo}} = 70$ (−70 °C), from which the difference in free energy of activation for the two competing reactions was calculated ($\Delta\Delta G^\ddagger_{-70^\circ\text{C}} = 1.70 \pm 0.02$ kcal mol^{−1}). The energy difference between the two transition states was very similar to, but slightly larger than, the ground state energy difference between the two conformations of the product. The authors conclude that the

relative stability of the conformational isomers of the product are amplified slightly in the transition state leading to them.

Since these initial investigations, Lewis acid catalyzed type 2 IMDA reactions have proven to be extremely valuable for inducing the reaction of complex Diels–Alder precursors.

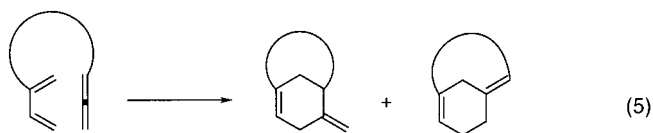
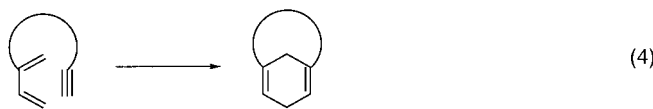
3.1.3. Acetylenic and Allenic Dienophiles—Synthesis of Bridgehead Dienes

Alkyne and allene dienophiles provide a greater thermodynamic driving force for the Diels–Alder cycloaddition (Table 6). In the type 2 intramolecular variant, this consid-

Table 6. Thermodynamic values for bimolecular Diels–Alder cycloadditions.^[15]

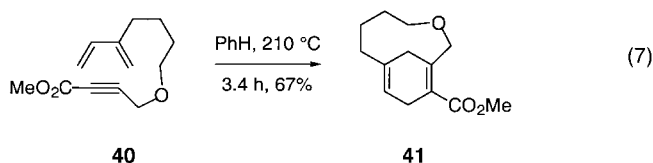
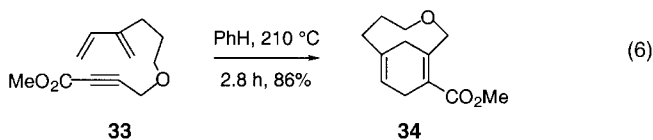
Reaction Components	Cycloadduct	ΔH° [kcal mol ^{−1}]	ΔS° [cal K mol ^{−1}]
		−40.5	−44.8
		−52.4	−42.6
		−50.0	−42.0

eration must be balanced by the greater strain energy in the cycloadduct. Cycloaddition in either case results in formation of bridgehead dienes, molecules that contain two non-conjugated bridgehead double bonds that are held in close proximity [Eq. (4) and (5)].^[14]



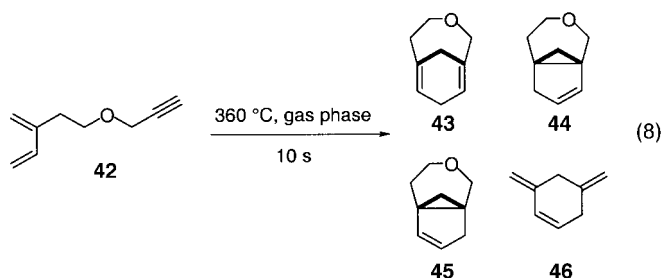
3.1.3.1. Acetylenic Dienophiles

The first examples employing acetylenic dienophiles are shown in Equations (6) and (7). The cycloaddition of dienyne esters **33** and **40** affords high yields of bridgehead diene



cycloadducts **34** and **41**.^[16] The reactions proceed in good yield to produce stable bridgehead diene esters. Solid derivatives, suitable for X-ray structure analysis, provided structural data for the two bridgehead double bonds.^[17]

The enthalpy change for a Diels–Alder cycloaddition of butadiene and acetylene is approximately $\Delta H \approx -52 \text{ kcal mol}^{-1}$ (see Table 6). This exothermicity can provide the thermodynamic driving force for the formation of very highly strained organic molecules. The current limit of an isolable molecule of this type is cycloadduct **43**, a highly reactive bridgehead diene formed by cycloaddition of diyne **42** [Eq. (8)].^[18] Diene **43** has a half-life of several hours at 0 °C

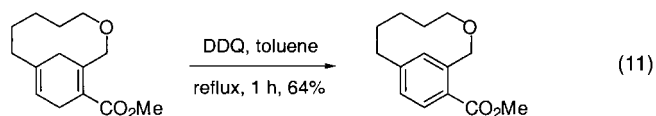
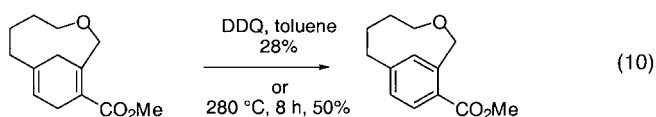


in dilute benzene solution. It is a derivative of *trans,trans*-1,4-cyclononadiene and contains two highly distorted bridgehead double bonds. The smaller, more highly strained bridgehead dienes will, at elevated temperatures, undergo reactions that alleviate the source of strain. For example, bridgehead diene **43** was found to undergo a homodienyl 1,5-hydrogen shift under the reaction conditions resulting in formation of propellanes **44** and **45**. Interestingly, the usual homo-1,5-hydrogen shift is in the direction of cyclopropane ring cleavage. In the above example, hydrogen transfer results in formation of a cyclopropane ring with concomitant loss of both bridgehead double bonds. Triene **46** was found to arise from both a 10-electron pericyclic reaction from bridgehead diene **43** and also a cleavage reaction of the cyclopropyl bond and extrusion of formaldehyde from the propellanes **44** and **45**.

Another striking illustration is found in Equation (9). Cycloaddition of diyne **47** results in formation of bridgehead diene **48**, a molecule containing a *trans,trans*-1,4-cyclo-

45 kcal mol⁻¹,^[20, 21] thus, the bulk of the reaction exothermicity has been stored as strain energy in the cycloadduct. Although pericyclic reactions are not usually employed for the synthesis of strained molecules, the preceding examples reveal that the strong exothermicity can provide new strategies for the synthesis of strained anti-Bredt alkenes.

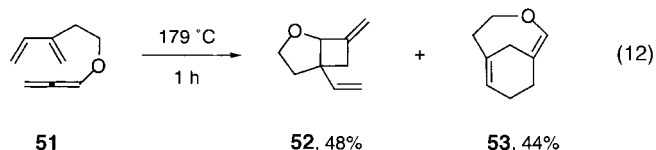
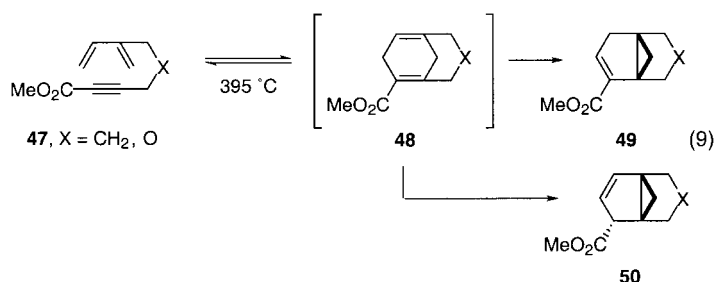
2,4-Bridged-1,4-cyclohexadienes that are spanned by larger rings exhibit thermal chemistry more characteristic of 1,4-cyclohexadienes. For example, extrusion of hydrogen to produce metacyclophanes [Eq. (10) and (11)] are representative examples.^[22]



3.1.3.2. Allene Dienophiles

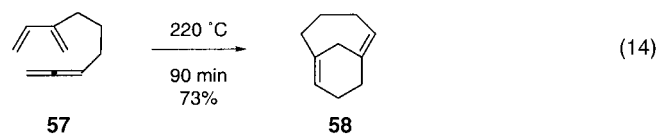
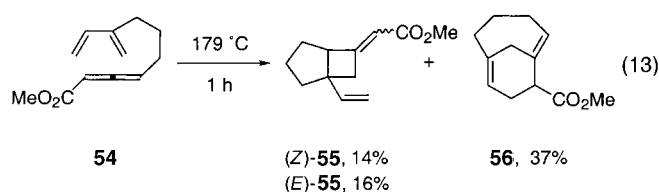
The reaction of butadiene with allene is calculated to be strongly exothermic, only slightly less exothermic than that with acetylene (Table 6). Type 2 IMDA reactions with allene dienophiles can undergo two modes of cycloaddition. In the first mode, reaction with the distal double bond gives rise to a bridged bicyclic skeleton containing two nonconjugated bridgehead double bonds constrained in a criss-cross arrangement [see Eq. (5)]. In the second mode, reaction of the proximal double bond gives rise to a bridgehead alkene containing an exocyclic double bond. A further complication arises from the fact that allenes can also react as 2 π -electron donors in [2+2] cycloadditions.^[23] Experimentally, all three reaction modes have been observed in allene–diene cycloadditions. Selected examples are shown in the equations below.

Thermolysis of 1,2-propadienyl-3-methylene-4-pentenyl ether (**51**) gives two major products, **52** and **53** in a combined yield of 92 % [Eq. (12)].^[24] The major product, an oxabicyclic

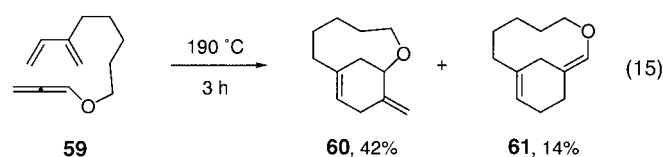


octadiene ring.^[19] The cycloadduct does not accumulate under the reaction conditions, rather it undergoes a homo-1,5-hydrogen shift to produce an isomeric pair of [3.3.1]propellanes, **49** and **50**. A single isomeric ester **50** (*endo*) is consistent with exclusive migration of the C-3 *exo* hydrogen atom. Estimates of the strain energy in **48** range from 35–

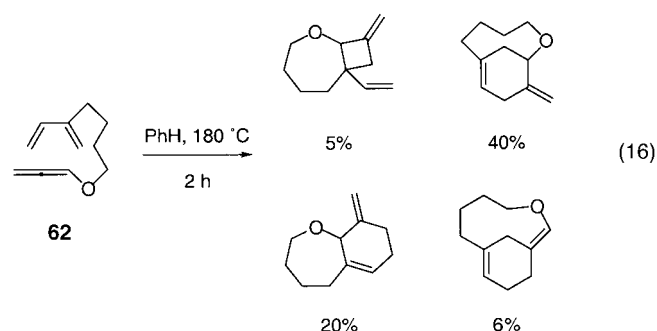
10[3.2.0]heptane, arises from a formal [2+2] cycloaddition of the diene and allene moieties of **51**. The minor cycloadduct, 3-oxabicyclo[4.3.1]deca-1,6-diene **53**, contains a *trans,trans*-cyclononadiene embedded in the bicyclic ring structure. This product arises from a [4+2] cycloaddition of the diene with the distal double bond of the allene. An activated allene in the carbocyclic series results in a somewhat faster rate of reaction but with similar distribution of [4+2] and [2+2] cycloadducts [Eq. (13)]. In contrast, the “parent” hydrocarbon 7-methylene-1,2,8-nonatriene (**57**) gave exclusively [4+2] cycloadduct **58** [Eq. (14)].



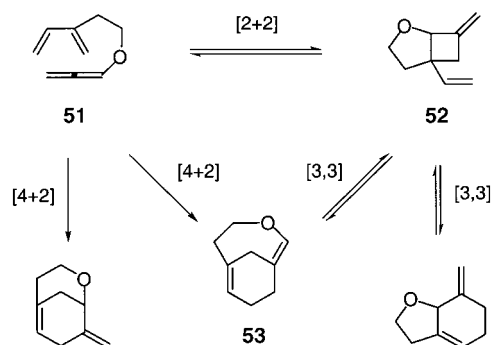
The introduction of additional atoms in the tether joining diene to allene results in the formation of new product mixtures. For example, the six-atom-bridged ether **59** gave [4+2] cycloadducts arising from cycloaddition to both proximal and distal double bonds (**60** and **61**) [Eq. (15)]. The five



-atom-bridged ether **62**, on the other hand, gives no less than four cycloaddition products, two each from the [4+2] and [2+2] cycloaddition modes [Eq. (16)].



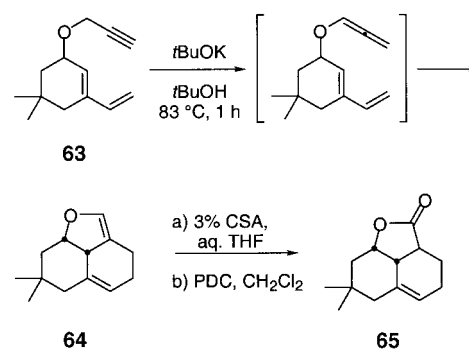
Several kinetic studies have established the dynamics between the reactants and products. Scheme 4 shows one such interrelationship between starting material **51** and the



Scheme 4. Interconversion of reactant **51** and products **52** and **53**.

two major products **52** and **53**. At 190 °C, there was a rapid build up of the [2+2] cycloaddition product followed by a slower accumulation of the [4+2] product. Thermolysis of an enriched sample of **53** (210 °C, 89 min, toluene) resulted in an equilibrium mixture of cycloadducts **52** and **53** (32:68). The two products were interconverted under the reaction conditions. Kinetic studies of the rate of disappearance of **51** and interconversion of **52** and **53** suggest the direct interconversion pathway is viable but may not be exclusive. There are at least two pathways interconnecting the two products **52** and **53**, one involves an equilibrium between the starting material and [2+2] cycloadduct (retro [2+2]), and the second a formal [3,3] sigmatropic rearrangement between **52** and **53**.

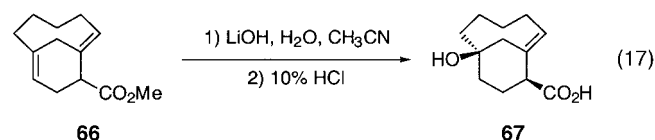
The synthesis of tricyclic lactones via intramolecular allene cycloaddition was reported by Kanematsu et al.^[25] Treatment of propargyl ether **63** with base at elevated temperatures resulted in the formation of cycloadduct **64** (Scheme 5). The



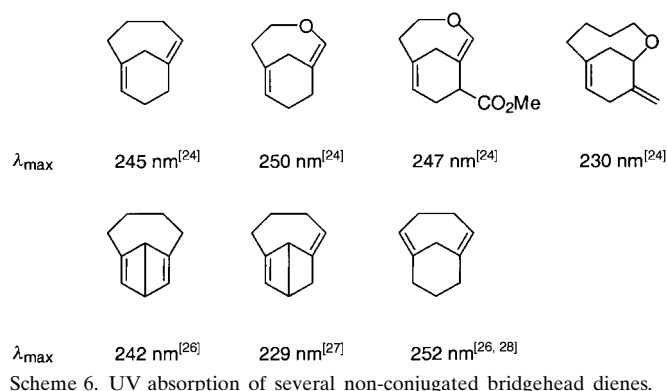
Scheme 5. Kanematsu's approach to tricyclic compounds using an allene dienophile. CSA = camphorsulfonic acid, PDC = pyridinium dichromate.

product arises from in situ isomerization to the allene intermediate followed by cycloaddition. Tricycle **64** was then hydrated and oxidized to produce the corresponding tricyclic lactone **65**.

The bridgehead dienes formed in the preceding examples have exceptional chemical and spectroscopic properties. For example, during efforts to saponify carboxylate ester **66** the more reactive bridgehead double bond underwent hydration [Eq. (17)].^[24] An X-ray crystal structure of product **67**



confirmed the chemo- and regiochemistry of the addition. Bridgehead dienes were found to have UV spectra that indicate transannular interactions between the two formally nonconjugated double bonds. Although simple trisubstituted nonconjugated double bonds rarely have UV absorption maxima above 200 nm, bridgehead dienes can have significant absorption maxima extending to greater than 250 nm. Several examples are included in Scheme 6.

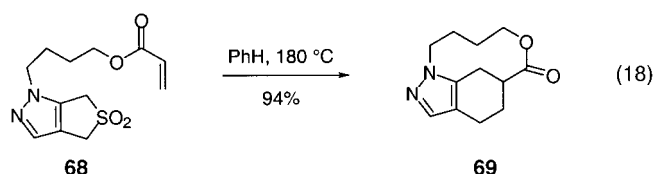


Scheme 6. UV absorption of several non-conjugated bridgehead dienes.

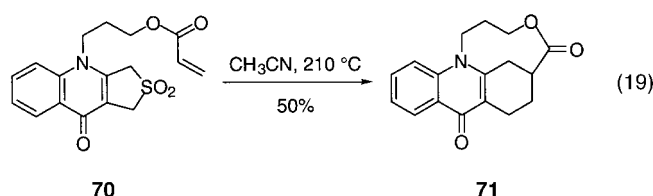
3.2. Masked Dienes and Dienophiles

A consequence of the reactivity of 2-substituted dienes is that they may have limited compatibility with some synthetic transformations. In these cases, a strategy to overcome this would be to append this fragment last or to utilize a masked diene that is liberated before or during the intramolecular Diels–Alder step.

Chou and Chen successfully used heterocycle-fused 3-sulfonenes as masked dienes in the type 2 IMDA cycloaddition. Thermolysis of **68** at 180 °C for 4 h produced the intermediate diene by extrusion of SO₂ which underwent a type 2 IMDA reaction to give pyrazole **69** [Eq. (18)].^[29] Chou and Chen also



synthesized a 2-substituted diene in a similar manner to effect the first type 2 IMDA cycloaddition of an *o*-quinodimethane. Thermolysis of **70** at 210 °C led to the formation of tetracycle **71** [Eqs. (19)].^[30]

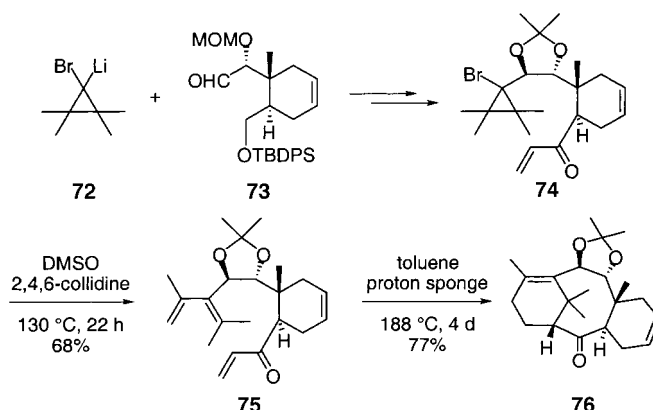


2-Metallo 1,3-butadienes are common precursors to 2-substituted dienes. Unfortunately, their reactions with electrophiles suffer from competing reaction of the metalloallenes, which are in equilibrium with the diene [Eq. (20)].^[31] To

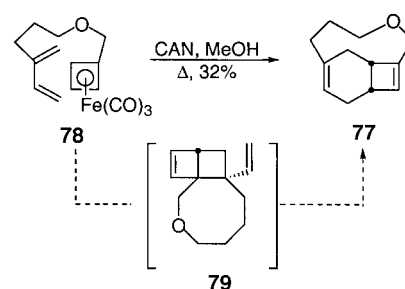


circumvent this problem, a 1-bromo-1-lithiocyclopropane was utilized as a masked diene for the synthesis of an advanced taxusin intermediate. Bromolithiotetramethylcyclopropane

(**72**) was added to aldehyde **73** and subsequently converted to enone **74** (Scheme 7).^[32] Liberation of highly methylated diene **75** and thermolysis of the product at 188 °C provided taxusin intermediate **76** in 77 % yield.

Scheme 7. Synthesis of advanced taxusin intermediate **76**.^[32]

In addition to employing masked dienes in the type 2 IMDA reaction, reactive dienophiles can also be sequestered until needed. This approach was used by Snapper and Limanto to carry a tricarbonylcyclobutadieneiron in the synthesis of bridged bicyclic product **77** (Scheme 8).^[33] Slow

Scheme 8. Synthesis of tricyclic adduct **77**.^[33] CAN cerium(IV) ammonium nitrate

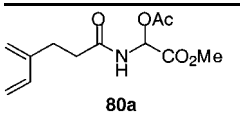
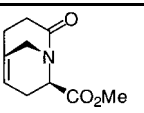
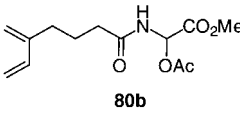
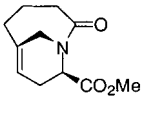
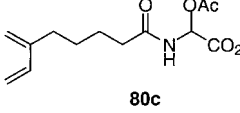
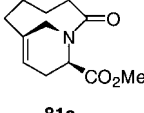
addition of **78** to a refluxing methanolic solution of a large excess of CAN (55 equiv) resulted in a 32 % yield of **77**. (It should be noted, however, that compound **77** could have arisen from a [2+2] cycloaddition producing **79**, followed by a Cope rearrangement.)

4. Hetero Diels–Alder Reactions

The heteroatom variant of the type 2 IMDA reaction can result in formation of bridged heterocycles in a single step from an acyclic precursor. This strategy was first recognized for the synthesis of bridgehead lactams.

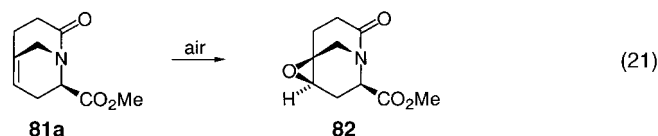
The type 2 intramolecular acyl imino Diels–Alder reaction was utilized as an entry to a class of compounds that possess both a bridgehead alkene and bridgehead lactam unit. Thermolysis of acetoxyamides **80a–c** produced intermediate *N*-acylimines which underwent subsequent cycloaddition to yield cycloadducts **81a–c** (Table 7).^[34, 35] Compound **81a** is

Table 7. Intramolecular acyl iminium Diels–Alder cycloadditions.

Starting material	Conditions ^[a]	Products	Yields [%] ^[b]
 80a	250 °C, 2 min	 81a	29
 80b	200 °C, 2 h	 81b	82
 80c	215 °C, 2 h	 81c	76

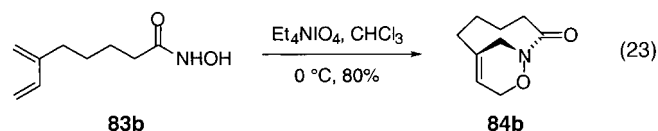
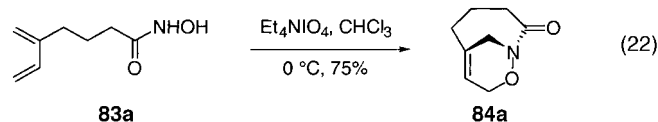
[a] Reactions were performed in xylenes at 0.01 M. [b] Yields refer to isolated products after chromatography.

one of the most highly strained isolable bridgehead alkenes prepared to date. The high reactivity of this compound is demonstrated by its spontaneous air oxidation to form epoxide **82** [Eq. (21)]. The crystalline nature of the bridge-



head lactams have provided structural data for both torsionally distorted bridgehead double bonds and bridgehead lactams (see Section 6).

Type 2 hetero Diels–Alder reactions have also been examined using *N*-acyl nitroso dienophiles. The *N*-acylnitroso dienophile is generated in situ by the oxidation of the corresponding hydroxamic acids. Cycloaddition occurs under mild conditions due to the high reactivity of the *N*-acylnitroso dienophile. The reaction is demonstrated by the cycloadditions of Diels–Alder precursors **83a** and **83b**.^[36] In situ generation of the acylnitroso functionality by periodate oxidation provide bridged oxazinolactams **84a** and **84b** [Eqs. (22) and (23)].

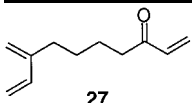
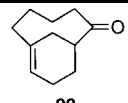
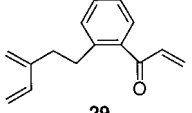
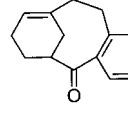
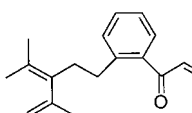
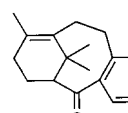


5. Kinetic Studies

Relatively few kinetic studies of the intramolecular Diels–Alder reactions have been reported.^[37] The little information available suggests that in addition to the expected kinetic advantages of intramolecularity that can arise from entropic factors, the nature of the intervening tether can exert a significant influence on the intramolecular reaction. This may be advantageous or deleterious to the overall rate depending on the nature of the connector.

One example is illustrated in the cycloaddition of triene ketone **25**.^[38] A comparison of the half-lives of cycloaddition for the series shown in Table 8 reveals that the introduction of

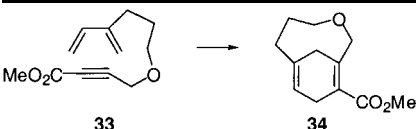
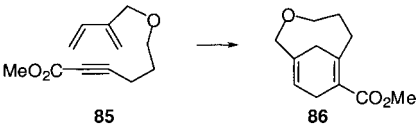
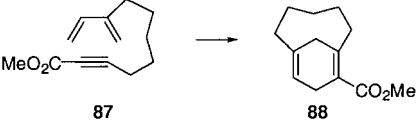
Table 8. Comparison of the half-lives of trienes **27**, **29**, and **38**.

Starting material	Product	$\tau_{1/2}$ h (T [°C])
 27	 28	15 (155)
 29	 30	1 (65)
 38	 39	18 (155)

two sp^2 centers in the tether can result in a rate enhancement of 10^6 . There are several factors that contribute to this rate enhancement. The most important may be the reduced conformational freedom on transition from **27** to **29** resulting from the introduction of three methyl groups including a *cis*-alkene linkage in the tether joining diene and dienophile in **29**. It was also noted, however, that aryl vinyl ketones are approximately 70 times more reactive than methyl vinyl ketone. This factor also contributes to the 10^6 fold increase in the reaction rate. In contrast to enhanced reactivity resulting from conformational restrictions, the reactivity of the system is dramatically reduced upon introduction of a *cis*-methyl substituent on the diene.^[39] This can produce up to a 10^6 fold decrease in the rate of cycloaddition (cf. the reaction of **38** in Table 8).

In our group we have reported a systematic investigation of the effect of tether length and the location of heteroatoms on the rate and activation energy parameters for the intramolecular cycloaddition of alkyndienyl ethers **33**, **85**, and **87** (Table 9).^[40] At 210 °C, diyne ether **33** is approximately 60 times more reactive than isomer **85** and the hydrocarbon analogue **87**. The activation energies for the cycloadditions are summarized in Table 9. The entropies of activation are, within experimental error, identical for all three reactions. Thus the rate differences between **33** and **85** and **87** are enthalpic in

Table 9. Influence of tether length and heteroatom location on the activation energy and enthalpy of diyne cycloaddition reactions.

Reaction	k_{rel} (210 °C)	$E_a^\ddagger$ [kcal mol ⁻¹]	$\Delta S^\ddagger$ [cal K mol ⁻¹]
 33 → 34	62	23.6	–28
 85 → 86	1	27.0	–29
 87 → 88	1	27.1	–29

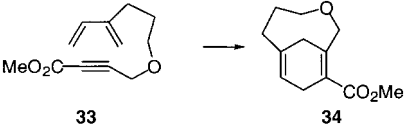
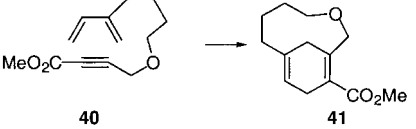
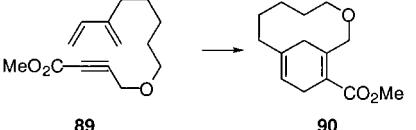
origin. An analysis of models of the transition state revealed the homopropargylic position in the tether and the diene hydrogen atoms of the exocyclic methylene group are in close proximity (Figure 1). In diene ether **33**, the homopropargylic

Figure 1. Proposed transition states for the cycloaddition of **33** and **87**.

position of the tether is occupied by an oxygen atom but in **85** and **87** the position is occupied by a methylene group. The well-documented difference in steric demands between an oxygen lone pair and a C–H bond was attributed in part to raising the activation energy for **85** and **87** over that of **33**.

The effect of tether length on the rate of cycloaddition was examined for the alkynyldienyl ethers **33**, **40**, and **89** (Table 10). At 210 °C, the rates of cycloaddition of **33** and **40** are approximately equal, while the rate of the seven-atom homologue **89** falls off to approximately one fifth of the

Table 10. Relative rates and activation energy parameters for the intramolecular Diels–Alder cycloaddition of alkynyldienyl ethers.

Reaction	k_{rel} (210 °C)	$E_a^\ddagger$ [kcal mol ⁻¹]	$\Delta S^\ddagger$ [cal mol ⁻¹]
 33 → 34	5.4	23.6	–28
 40 → 41	5.5	20.6	–35
 89 → 90	1	22.6	–34

reference compound **33**. Analysis of $E_a^\ddagger$ and $\Delta S^\ddagger$ revealed no simple trends. As the tether length increases through the series, the activation entropy ($\Delta S^\ddagger$) levels off after an initial increase in tether atom number from five to six. It was proposed that in a series of this type with a progression of tether lengths, perhaps only three or four bonds need to be “frozen” in the transition state. The residual bonds can remain floppy and not extract an entropic price in the transition state entropy. Similar leveling off effects in entropy have been

noted in macrocyclization reactions.^[41] The activation energy $E_a^\ddagger$ on the other hand follows no pattern. This is not surprising since competing contributions are at work. For example, product steric energy decreases with increasing tether size. This can result in a change in the transition state from late to early modulating the contribution of nonbonding interactions in the transition state. The absence of a monotonic trend in both enthalpy and entropy of activation emphasizes the diversity of contributions to these terms that can complicate the ability to predict kinetic trends even within a closely related series of reactants.

The study also included an evaluation of the effective molarity (EM) of the cycloaddition **40** → **41** [see Eq. (7)]. A comparison of rate constants with the bimolecular counterpart gave an EM of ≈ 0.4 – 0.5 M, a relatively modest kinetic advantage compared with other intramolecular reactions.^[42]

6. Structural Studies of Bridgehead Alkenes

Type 2 IMDA reactions provide a general route to substituted bridgehead alkenes and dienes and has made available a number of crystalline derivatives for X-ray structure analysis. The distinguishing substructural feature of a bridgehead alkene is the *trans*-cycloalkene (**91**, Figure 2) that is embedded in the bridged bicyclic structure. The double bond is subjected to a torsional distortion that twists the π bond out of coplanarity resulting in loss of overlap of the 2p orbitals. In response to this torsional distortion, the sp^2 carbon atoms also undergo rehybridization by incorporating s character into the p orbitals of the π bond. This results in pyramidalization of each of the sp^2 carbon atoms.

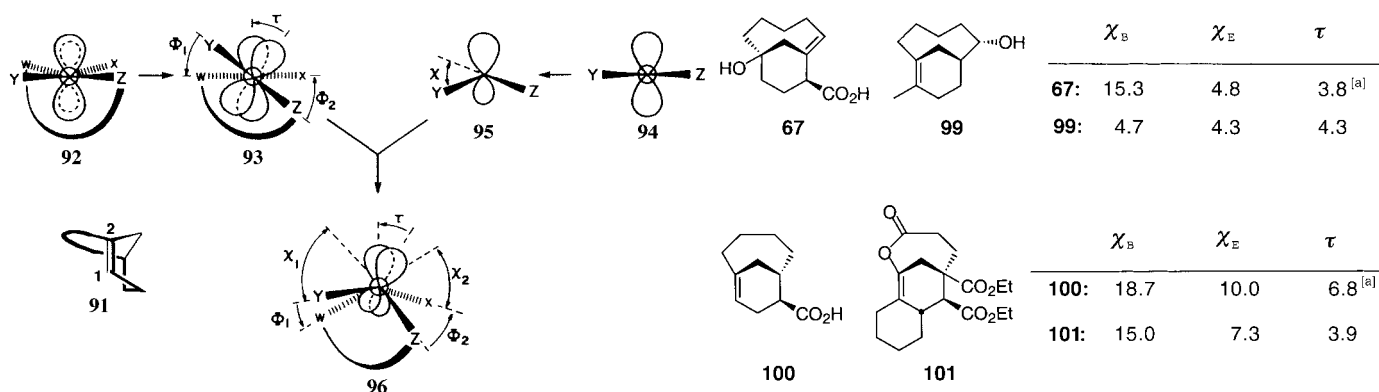


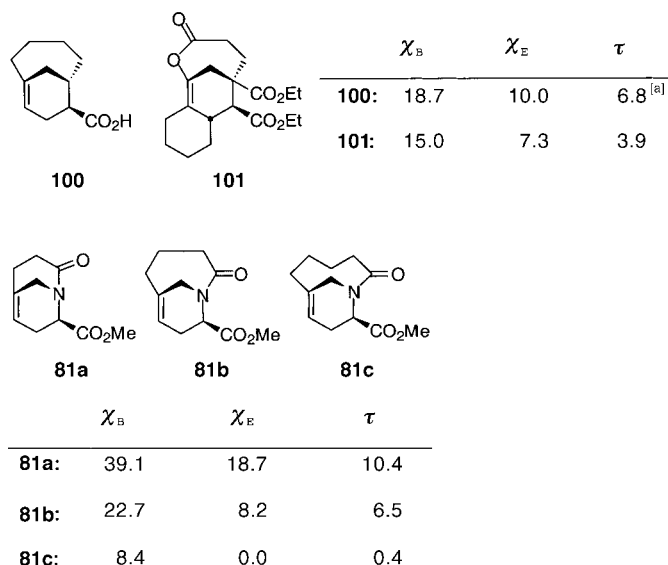
Figure 2. Analysis of the distortional parameters χ and τ , for a torsionally distorted double bond.

The extent of these distortions can be quantified by the torsion angle τ between the p orbitals of the double bond and the pyramidalization angle χ of the constituent atoms of the π system (see Figure 2).^[43] The view along the C1–C2 axis of π -system 91 is represented by 92. Rotation of C1 relative to C2 produces a misalignment of the p orbitals of the π bond (93). The torsional deformation is quantified by the angle τ between the axes of the two p orbitals. The torsional angle τ is not directly measurable by X-ray crystallography but may be determined by measuring either of the four atom torsional angles YC_1C_2W (Φ_1) or ZC_1C_2X (Φ_2).

The two atoms of the π system rehybridize independently. Incorporation of s character into the π bond p orbital (rehybridization) produces a pyramidalized atom 95. The degree of the pyramidalization of each atom is quantified by the pyramidalization angle χ (see 95). For an $sp^{2.00}$ atom, χ is 0.0° , while for an $sp^{3.00}$ atom χ is 60.0° . In the composite structure 96, Φ_1 and Φ_2 are no longer equivalent so the torsional distortion τ is defined as the average by the equation $\tau = (\phi_1 + \phi_2)/2$. Structural data for a number of bridgehead alkenes have been summarized in a review.^[44] Selected examples, chosen to illustrate the degrees of distortion found in various bridgehead alkenes, are given below.

The magnitude of both pyramidalization (χ) and torsional distortion (τ), are modest for bridgehead alkenes with five or more atoms in the tether. In these ring systems the *trans*-cycloalkene is in a ten-membered ring or greater.^[44] Two bicyclo[5.3.1]undecenes, 67 and 99, illustrate this point (Scheme 9). The bridgehead double bonds in 67 and 99 each have τ values of approximately 4° , and only the bridgehead carbon atom in 67 experiences more than negligible pyramidalization. As a consequence of these slight distortions, the reactivity of the bridgehead double bond is unexceptional.

Both pyramidalization and torsional distortion increase in the bicyclo[4.3.1] ring system (see data for structures 100 and 101 in Scheme 9).^[44] The pyramidalization at both sp^2 carbon atoms is real and the τ values are 3.9 and 6.8° , respectively. Some of the most serious distortions are found in the bicyclo[3.3.1] ring system. The trends in the distortion are best observed in the homologous series of bridgehead alkene/lactams, 81a–c (Scheme 9 and Figure 3).^[35] Successive removal of a methylene group produces a corresponding increase in the value of χ at both carbon atoms and an



Scheme 9. Geometric distortions of bicyclo[5.3.1]undecenes 67 and 99, bicyclo[4.3.1]decenes 100 and 101, and the homologous alkenes 81a–c. χ_B corresponds to the pyramidalization of the bridgehead carbon, χ_E corresponds to the pyramidalization of the exocyclic carbon. [a] Average derived from calculated hydrogen atom position in the X-ray crystal structure.

increase in τ . The distortions in 81a are some of the largest reported.

The series of molecules also has a bridgehead lactam, a quasi double bond that responds similarly to the progressive distortions (Figure 4, Table 11). Due to the softer bending potential of nitrogen, the bridgehead nitrogen atom experiences complete pyramidalization. Interestingly unlike the C–C double bond which shows no variation in length upon increased torsional distortion, the C–N bond in 81a is several hundredths of an angstrom longer than in 81b and 81c.

The geometric distortions noted in the bicyclo[4.2.1] and [3.3.1] ring systems are paralleled by an increase in chemical reactivity. Bicyclo[3.3.1]nonenes are more than $>10^6$ times more reactive than the less highly strained bridged alkenes in electrophilic additions to the double bond.^[45, 46]

7. Application of the Type 2 IMDA Reaction in Syntheses

The synthetic utility of any reaction is determined by the ability to control or limit the formation of isomeric products. Despite the enormous importance of the Diels–Alder reaction, isomer control remains as a serious limitation to its effective employment in solving synthetic problems. The type 2 IMDA reaction provides strategies for the solution of these problems.

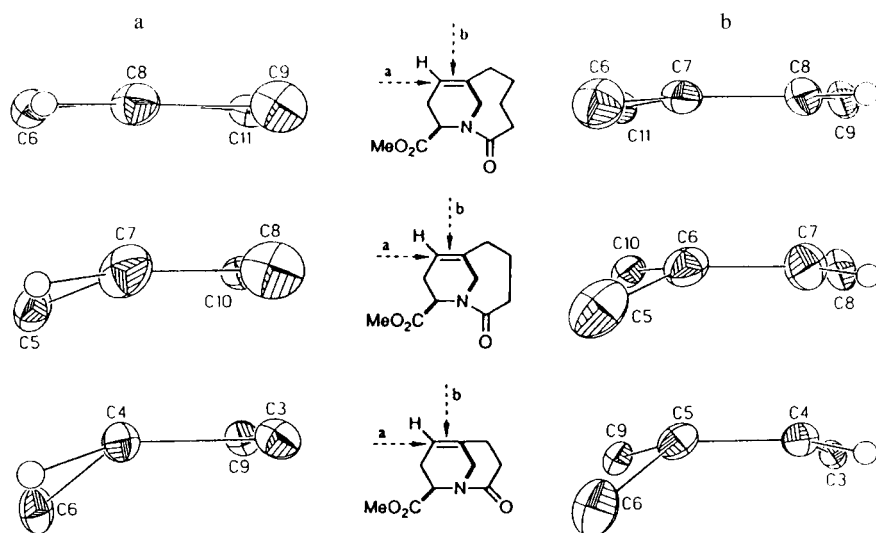


Figure 3. ORTEP plots (at 20% probability level for clarity) of the bridgehead alkene bonds and their substituents for **81a–c** with all other atoms omitted. a) Alkenes viewed along the axis of the C=C double bond with the exocyclic alkene carbon atom in front (indicated by dashed arrows a in the formulas). b) Side views (indicated by dashed arrows b in the formulas).

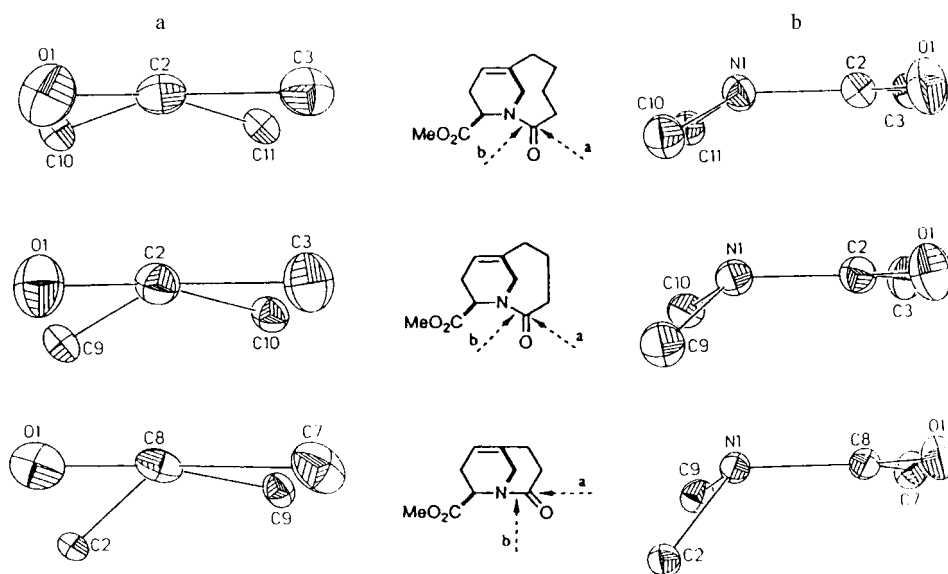


Figure 4. ORTEP plots (at 20% probability level for clarity) of the bridgehead lactam bonds and substituents for **81a–c** with all other atoms omitted. a) Lactams viewed along the axis of the C–N bond with the carbonyl carbon atom in front (indicated by dashed arrows a in the formulas). b) Side views (indicated by dashed arrows b in the formulas).

Table 11. Geometric distortions of homologous lactams **81a–c**.

Compound	$\chi_N^{[a]}$	$\chi_C^{[a]}$	τ	$d(\text{C–N})$ [Å]
81a	54.9	1.6	16.7	1.399
81b	46.5	1.1	7.5	1.374
81c	38.1	0.1	0.9	1.377

[a] χ_N corresponds to the pyramidalization of the bridgehead nitrogen atom, χ_C corresponds to the pyramidalization of the carbonyl carbon atom.

The type 2 IMDA reaction affords a general method for controlling the regio- and stereochemistry of the cycloaddition. In addition, by incorporation of a stereocenter in the triene precursor, the reaction allows discrimination between the diastereotopic faces of the reacting diene and dienophile.

Finally, the conformational rigidity of the resulting bridged cycloadducts allows their stereoselective elaboration. Analysis of these control elements is detailed in the sections that follow.

7.1. Regiochemical Control

Regioselectivity in bimolecular Diels–Alder reactions is understood in terms of FMO analysis. The dominant perturbation between a diene with a donor substituted in the 2-position and a dienophile containing an electron-withdrawing group results in a 1,4-substituted cycloadduct. Selectivities >95:5 are observed for a 2-oxy-substituted diene and methyl acrylate.^[47] This intrinsic regiochemical bias must be considered in anticipating the regiochemical outcome of any Diels–Alder reaction of this substitution pattern.

In contrast to the bimolecular reaction, the type 2 intramolecular Diels–Alder reaction exhibits a preference for formation of the *meta* cycloadduct. In small ring systems, this preference probably arises in part from the greater stability of the *meta* cycloadduct compared to the *para* cycloadduct since the *meta* regioisomer contains the *trans*-cycloalkene in the larger (less strained) ring (Figure 5). The *meta*–*para* energy difference diminishes as the ring size increases.^[48] Therefore, as the tether size is increased, the cycloaddition reactions are influenced by the usual steric, conformational, and electronic factors.

Analysis of a considerable body of experimental data provides the basis for several generalizations.

For tethers containing three, four, and five atoms, cycloaddition results in the *meta* regioisomer as the *exclusive* product regardless of the dieneophile's activation pattern.^[49] The cycloaddition of trienes **102** and **104** illustrate this point [Eqs. (24) and (25)].^[50] Lewis acid catalyzed cycloaddition of internal-

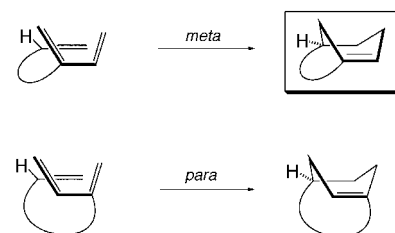
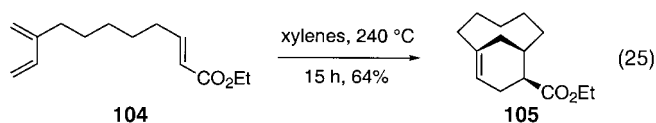
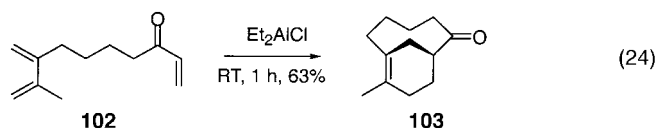


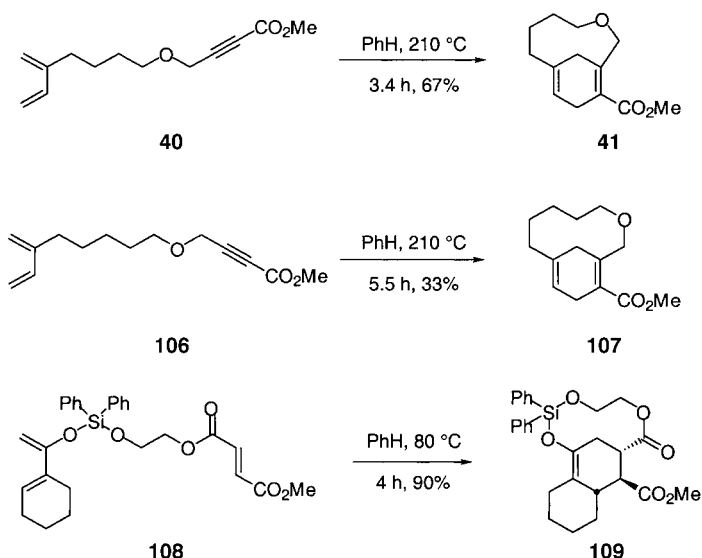
Figure 5. Regioadducts in the type 2 IMDA reaction.



ly^[51] activated triene **102** yields **103** as a single regioisomer. The thermal cycloaddition of externally^[51] activated ester **104** furnishes cycloadduct **105**, also as a single product.

A balance of electronic considerations (FMO analysis) and steric or conformational factors govern the regioselectivity of tethers with six or more atoms. Externally activated trienes furnish the 1,3-regioisomer exclusively. Six- and seven-atom dienynes **40** and **106** illustrate this point, both dienynes afford 1,3-substituted bridgehead dienes as the sole products (Scheme 10).^[18] Additionally, 1,2-diacetivated dienophiles also furnish 1,3-regioisomers as the sole product. For example, seven-atom-tethered fumarate **108** undergoes cycloaddition to produce **109** as a single product.^[52]

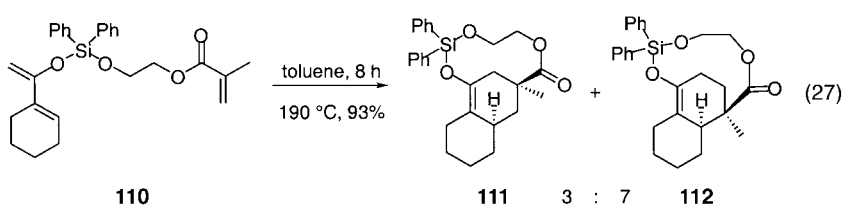
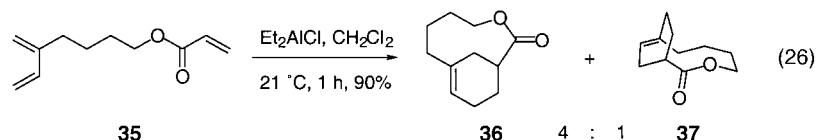
Internally activated dienophiles with six or more atoms in the tether can produce mixtures of regioisomers, whose ratio is determined by both the intrinsic biases of the reacting partners and conformational factors. For example, six-atom-tethered acrylate **35** undergoes Lewis acid catalyzed cycloaddition to afford the 1,3- and 1,4-regioisomers **36** and **37** in a 4:1 ratio [Eq. (26)].^[12] The Diels–Alder cycloaddition of 2-siloxy-substituted methacrylate **110** proceeds to furnish 1,3- and 1,4-substituted regioisomers **111** and **112** in a 3:7 ratio in favor of the 1,4-substituted regioisomer [Eq. (27)].^[53]



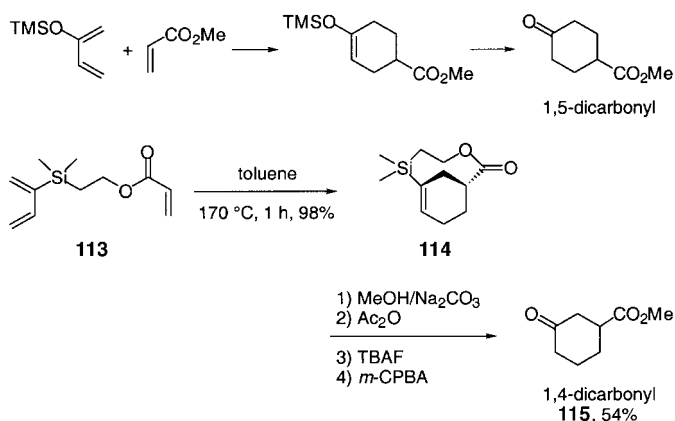
Scheme 10. Type 2 IMDA reactions of compounds in which the diene is tethered to the dienophile over six or seven atoms.

These concepts can be used to reverse the intrinsic regiochemical preferences of the intermolecular Diels–Alder reaction. This strategy, termed *pericyclic umpolung*, when coupled with disposable tether methodology, allows synthesis of cyclohexene derivatives with substitution patterns that are *reversed* from those from the bimolecular Diels–Alder reaction.^[53]

The synthesis of substituted cyclohexanones is used to illustrate this concept. Bimolecular cycloaddition of 2-oxo-substituted dienes with methyl acrylate results in predominant



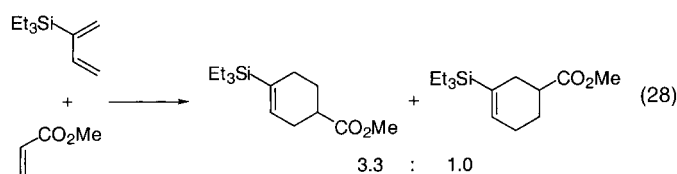
formation of the 1,4-cycloadduct (Scheme 11 top),^[47] whose hydrolysis affords a cyclohexanone product with a 1,5-dicarbonyl orientation. Temporary union of the two reactants



Scheme 11. Pericyclic umpolung applied to the synthesis of methyl 3-oxocyclohexanecarboxylate (**115**). The course of the normal Diels–Alder reaction is shown above. TBAF = tetrabutylammonium fluoride, *m*-CPBA = *meta*-chloroperoxybenzoic acid.

and cyclization provides complete regiochemical control to deliver the 1,3-regioisomer. This is demonstrated by the cycloaddition of vinyl silane **113** which affords cycloadduct **114** as the sole product. Oxidative tether cleavage produces methyl 3-oxocyclohexanecarboxylate **115**, with a 1,4-dicarbonyl orientation.

In the preceding example silicon was used as an oxygen surrogate. The choice of silicon provides a broader range of coupling strategies for the Diels–Alder precursor in addition to relaxing the intrinsic (1,4) regiochemical bias. The corresponding bimolecular reaction of 2-triethylsilyl-1,3-butadiene with methyl acrylate provides a 3.3:1.0 mixture of 1,4- and 1,3-regioisomers [Eq. (28)].^[54]



The patterns that emerge from these studies allow one to predict the regiochemical outcome of a type 2 IMDA reaction based upon tether length and the arrangement of activating groups on the reacting diene and dienophile. In addition to regioisomer control, the concept of pericyclic umpolung permits a completely revised analysis of synthetic strategies that employ Diels–Alder reactions for the synthesis of six-membered rings. These strategies have been reduced to practice in the context of natural product synthesis (see Section 8).

7.2. Stereochemical Control

The origins of stereoselectivity in the Diels–Alder reaction are attributed to secondary orbital interactions between the diene and dienophile. The magnitude of these interactions is typically less than several kcal mol^{−1}.^[55] Understandably, control of stereochemistry presents special challenges. Unlike type 1 intramolecular Diels–Alder counterparts [Eq. (1)], type 2 intramolecular Diels–Alder reactions show *complete stereoselectivity*. Cycloaddition takes place from a conformation where the tether occupies the endo position affording an “out”-bridged bicyclic adduct (Figure 6). The origin of this

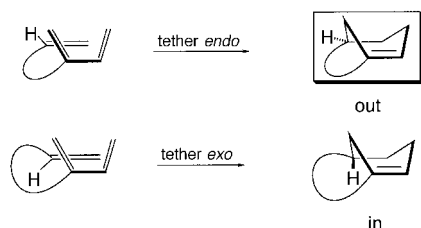
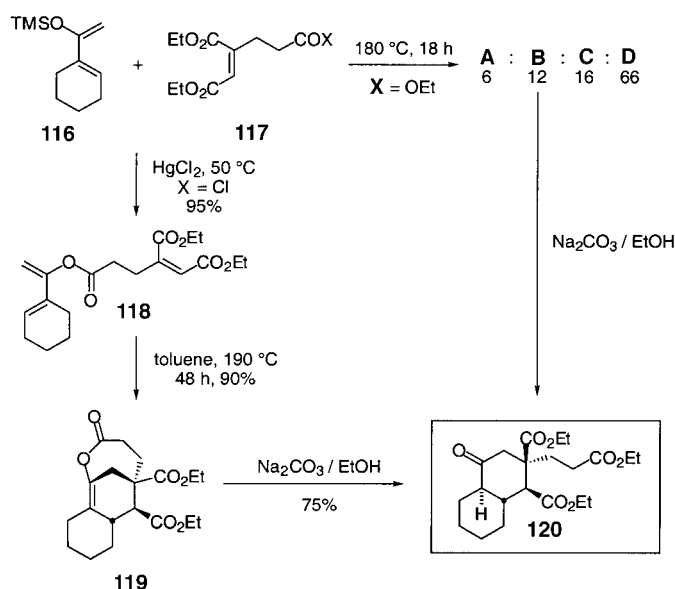


Figure 6. Stereoselectivity of the type 2 IMDA reaction.

preference is readily understood from consideration of the two possible stereoisomeric products. The tether *exo* stereochemistry results in formation of an in-bridged bicyclic adduct. In small- and medium-sized tethers ($n=3-7$), this stereoisomer is considerably higher in energy than the corresponding cycloadduct resulting from the tether *endo* arrangement. The transition states leading to these two stereoisomeric products reflect the relative differences of strain in the cycloadducts. This energy difference is considerable and overrides the contributions that arise from what are the usual determinants in stereochemical control, namely secondary orbital interactions. As a result, the type 2 cycloaddition gives products that arise exclusively from *endo* tether stereochemistry.

The utility of the stereochemical control inherent to the type 2 IMDA reaction is illustrated by the example in Scheme 12.^[56] The *bimolecular* cycloaddition of the dien-2-ol



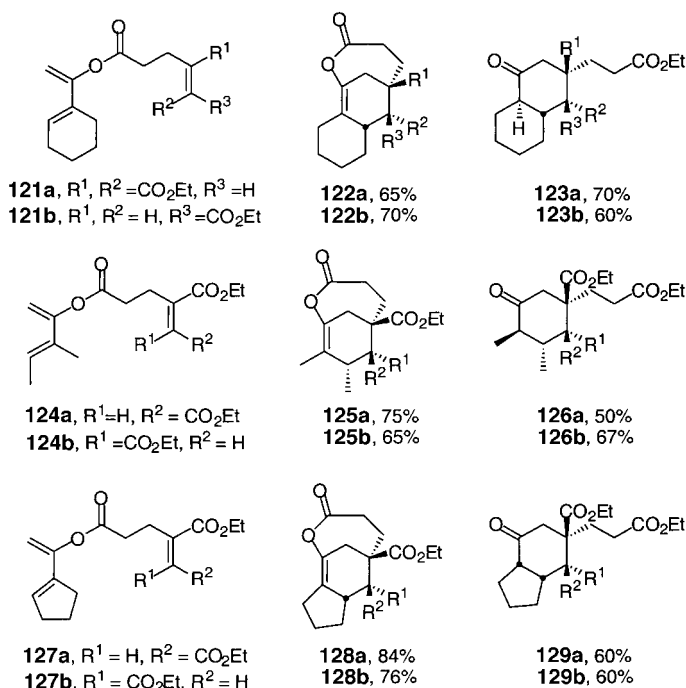
Scheme 12. Stereoselectivity of the type 2 IMDA reaction.

116 and the trisubstituted dienophile **117** results in formation of all four regio- and stereoisomers, **A**, **B**, **C**, and **D** (excluding enantiomers) in a ratio of 6:12:16:66. Synthetically, this reaction is useless. However, union of **116** and **117** in a type 2 manner affords Diels–Alder precursor **118**. Cycloaddition (190 °C, 48 h, toluene) results in formation of a *single cycloadduct*, **119**, a bridgehead enol lactone, in 90 % yield. The configuration of the three contiguous asymmetric centers was established unambiguously by X-ray crystallography. The reaction proceeds with *meta* regioselectivity and tether-*endo* stereochemistry to account for the relative configuration of the three contiguous asymmetric centers. Cleavage of the bridgehead enol lactone (Na₂CO₃, MeOH) produces the 1-decalone ring system **120**, which under the equilibrating conditions of the cleavage, gives rise to the thermodynamically controlled stereochemistry at the ring junction (*trans*-decalone).^[57] A minor product (<12 %) in the bimolecular cycloaddition, stereoisomer **B**, corresponds to the sole product of the type 2 IMDA reaction.

The combination of type 2 IMDA reaction followed by lactone cleavage and epimerization allows one to set, in a predictable manner, the relative configuration of four contiguous asymmetric centers and, in effect, select a single regio- and stereoisomeric product from an otherwise unproductive reaction. Selected ring systems and substitution patterns that have been synthesized by this approach are provided in Scheme 13.

7.3. Disposable Tethers between Diene and Dienophile: General Solutions for Controlling Regio- and Stereochemistry

The application of disposable tether methodology in the type 2 IMDA reaction provides a method for temporarily staging the Diels–Alder reaction to control the regioselectivity and stereoselectivity.^[58–60] This strategy capitalizes on

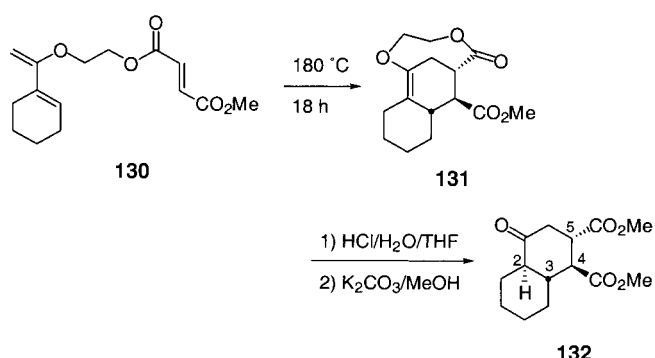


Scheme 13. Products of cycloadditions of enol lactones (left) before (center) and after (right) cleavage of the tether.

the inherent 1,3-regioselectivity of the type 2 IMDA reaction to provide, after removal of the tether, cyclohexene products that often correspond to the minor component formed in the corresponding bimolecular Diels–Alder reaction. The following sections review the types of tethers that have been used and present examples exploiting disposable tether methodology for controlling the regio-, stereo-, and enantioselectivity of the type 2 IMDA reaction.

7.3.1. Vinyl Ethers and Silyl Acetals

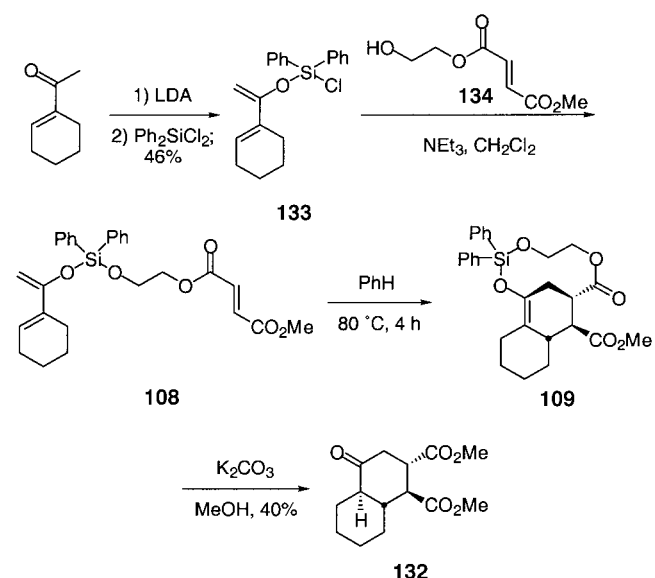
There are relatively few examples of vinyl ethers in the type 2 IMDA reaction (Scheme 14).^[52] Heating a solution of vinyl ether **130** furnished cycloadduct **131**. The cycloaddition



Scheme 14. A disposable vinyl ether linker in the type 2 IMDA reaction.

establishes the relative configuration of centers 3, 4, and 5. Subsequent hydrolysis followed by esterification sets the relative configuration at C2 to provide *trans*-decalin **132**.

A more common strategy for uniting the diene and dienophile is to use silicon-containing tethers. The first example of this utilized a silyl acetal linkage (Scheme 15).^[52] The reaction of dichlorodiphenylsilane with the enolate of 1-acetylcyclohexene gave the chlorosilyl enol ether **133**, followed by treatment with alcohol **134** yielded the Diels–Alder precursor **108**. The success of this strategy relies on the differential reactivity of the two chlorines in dichlorodiphenylsilane enabling the synthesis of mixed silyl acetals.^[61] Triene **108** was cyclized in benzene at 80 °C to give cycloadduct **109**, whose structure was confirmed by single-crystal

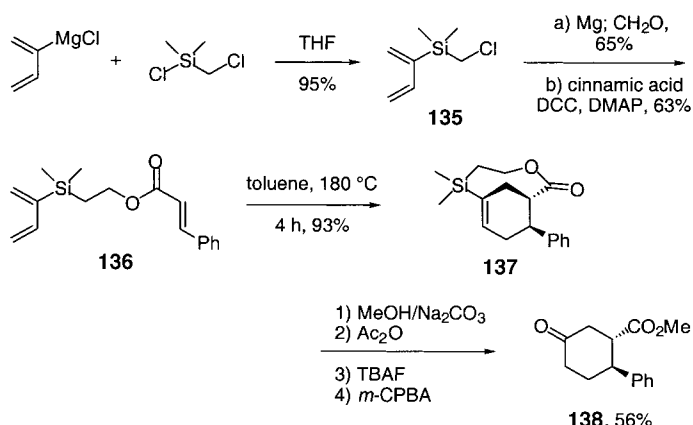


Scheme 15. The use of the silyl acetal linker in the type 2 IMDA reaction. Compound **109** was obtained in 53 % yield starting from **133**.

X-ray structure analysis. Methanolic cleavage of silyl acetal **109** leads to decalone **132**. The corresponding bimolecular cycloaddition gives an inseparable mixture of stereoisomers.

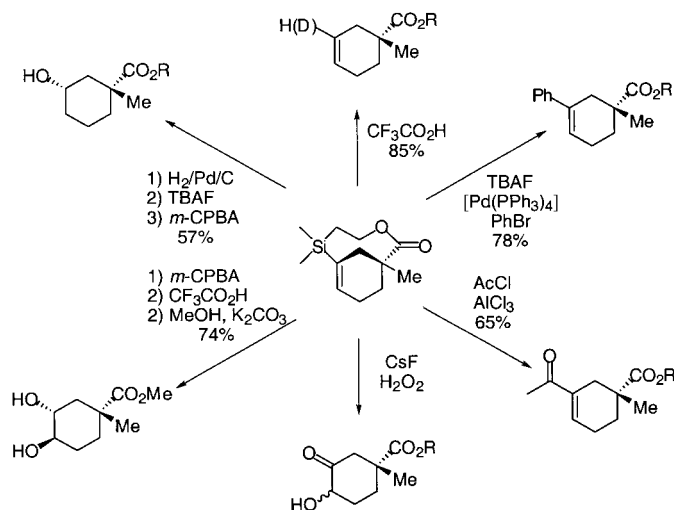
7.3.2. Vinyl Silanes

Vinyl silane tethers have also been utilized to temporarily join the diene and dienophile.^[53] The linker in Scheme 16 was synthesized from the chloroprene Grignard reagent and



Scheme 16. Synthesis of a cyclohexanone by using a vinyl silane tether. DCC = dicyclohexylcarbodiimide, DMAP = dimethylaminopyridine.

chloro(chloromethyl)dimethylsilane. The resulting diene product **135** is homologated by treatment with magnesium and formaldehyde. Acylation provided Diels–Alder precursor **136**. Cycloaddition of triene **136** in toluene at 180 °C for 4 h gave a 93 % yield of cycloadduct **137**. Oxidative tether cleavage of the carbon–silicon bond provides cyclohexanone **138** as a single regioisomer. The resulting bridgehead vinyl silane cycloadducts are cleaved under a variety of conditions to give substituted cyclohexane derivatives (Scheme 17).^[62, 63]



Scheme 17. Elaboration of bridgehead vinyl silanes.

7.3.3. Allyl Silanes

Allyl silane tethers have also been used to stage the type 2 IMDA reaction.^[64] The Diels–Alder precursors **140a–h** were synthesized from (chloromethyl)(hydroxymethyl)dimethylsilane (**139**) [Eq. (29); Table 12]. Using this chemodifferentiated linker, chloroprene and various dienophiles were joined in a multistep one-pot procedure. This sequence of reactions

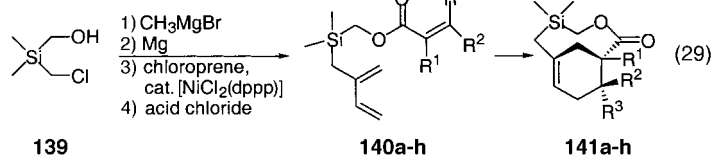


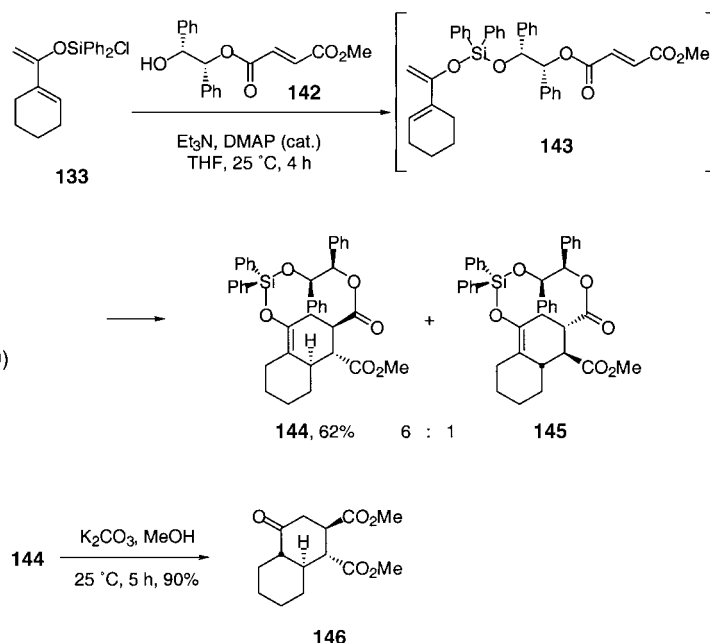
Table 12. Synthesis of allyl silane Diels–Alder precursors and their cycloaddition.

Compound	R ¹	R ²	R ³	Yield of 140 [%]	Yield of 141 [%]
a	H	H	H	92	80
b	CH ₃	H	H	82	90
c	H	CH ₃	H	95	94
d	CH ₃	CH ₃	H	90	77
e	H	Ph	H	89	96
f	CH ₃	Br	H	85	74
g	H	CO ₂ Me	H	71	75
h	CN	Ph	H	72	89

involved the formation of a Normandt–Grignard reagent from **139**, followed by a nickel(0)-catalyzed coupling with chloroprene and finally addition of an α,β -unsaturated acid chloride to form the desired trienes **140a–h**. The type 2 IMDA reactions of trienes **140a–h** were performed in heated sealed tubes in toluene with additives (proton sponge and 2,6-di-*tert*-butyl-4-methylphenol (BHT)). The cycloadditions occurred with complete regio- and stereochemical control (Table 12).

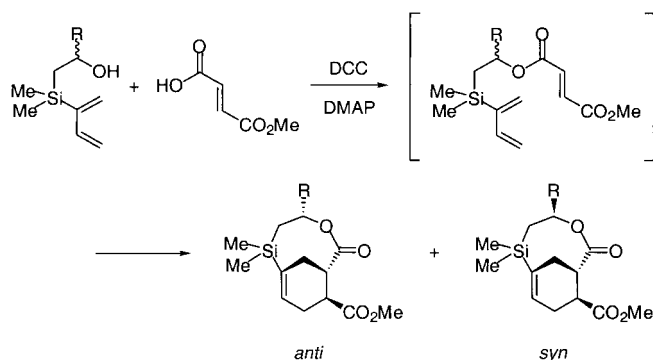
7.4. π -Facial Selectivity in the Type 2 IMDA

The disposable tether concept allows modularity of the linker joining the diene and dienophile. Introduction of an asymmetric segment on the tether provides an opportunity to influence the π -facial selectivity of the cycloaddition. An enantioselective decalone synthesis utilizing a chiral disposable tether illustrates this approach (Scheme 18).^[65] The diene and dienophile were joined by using the (+)-hydrobenzoin auxiliary **142** and the silyl enol ether **133**. Cycloaddition of **143** led to a pair of diastereomers, **144** and **145**, in a 6:1 ratio. Pure **144** was isolated by chromatography in 62 % yield. The absolute and relative configuration was determined by single-crystal X-ray structure analysis. Tether removal afforded *trans*-decalone **146** in 90 % yield and >99.5 % *ee*. Since both enantiomers of hydrobenzoin are readily available, this strategy allows the synthesis of the enantiomeric decalone **146**.



Scheme 18. Enantioselective synthesis of a decalone by the type 2 IMDA reaction.

The diastereoselectivity of the cycloaddition of vinyl silanes has also been studied (Scheme 19).^[62] Coupling of substituted vinyl silanes and methyl fumarate led to Diels–Alder precursors whose cycloaddition resulted in formation of



R	Conditions	Yields [%]	anti/syn
H	60 °C, 18 h	89	—
Me	65 °C, 13 h	77	3.1 : 1
Ph	65 °C, 16 h	54	4.2 : 1
<i>i</i> Pr	60 °C, 14 h	75	4.8 : 1
<i>t</i> Bu	25 °C, 18 h	75	9.4 : 1

Scheme 19. Diastereoselective synthesis of vinyl silane cycloadducts.

anti/syn diastereomers. Increased steric bulk of the substituent on the tether led to a higher level of diastereoselectivity.

7.5. Stereoselective Elaboration of Bicyclo[*n*.3.1] Ring Systems

The restricted conformational mobility of bridged bicyclic compounds permits their stereoselective elaboration. The following sections illustrate this concept with examples of functionalization of the bridgehead alkene and the medium-sized rings embedded in bridgehead bicyclo[*n*.3.1]alkenes.

7.5.1. Additions to the Bridgehead Double Bond

The torsional distortions associated with bridgehead double bonds can result in dramatic increases in chemical reactivity.^[45, 46] More importantly for the present discussion, additions to these bridgehead double bonds occur in a *syn* manner (Figure 7).^[2] Addition occurs exclusively from the *exo* face to

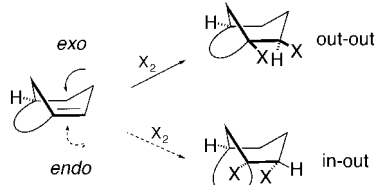
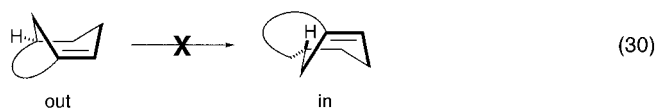


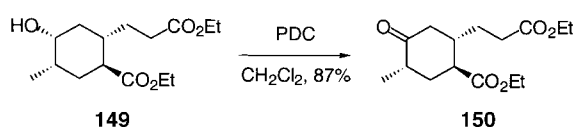
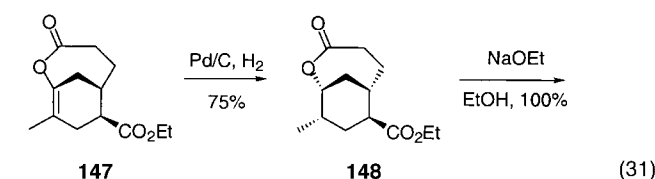
Figure 7. Stereochemistry of the addition to bridgehead double bonds.

give the out-out-bridged product rather than from the *endo* face to give the less stable in-out-bridged bicyclic product. The interconversion of the out-cycloadduct to the in-conformational isomer for short tether lengths is not energetically accessible; this process, referred to as homeomorphic isomerism, would involve movement of the one carbon bridge

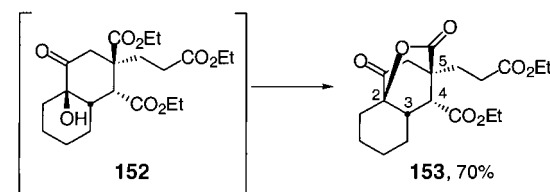
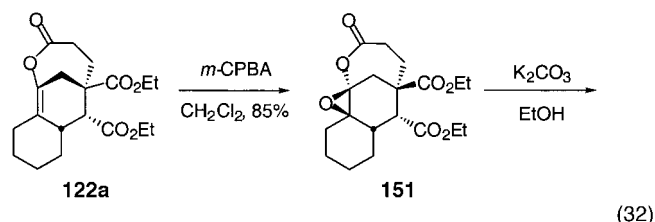
through the medium ring [Eq. (30)].^[66] The conformational integrity of the out-cycloadduct exposes only the *exo* face of the alkene to reagents.



As a result of these restrictions, reactions of the bridgehead double bond provide a stereocontrolled entry into functionalized six-membered rings. Two examples are shown in reactions (31) and (32). Hydrogenation of bridgehead enol



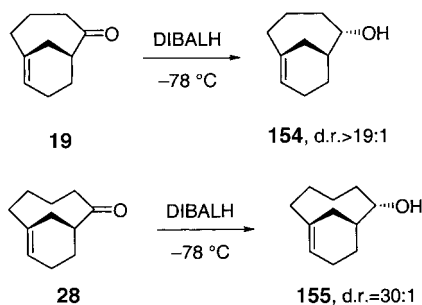
lactone **147** affords, after lactone cleavage, isomerically pure cyclohexane **149**.^[67] Subsequent oxidation provides cyclohexanone **150**. By comparison, the direct cleavage of **147** (NaOEt, EtOH) gives a mixture of **150** and its C-2 epimer in a 15:85 ratio.



In reaction (32) the bridgehead alkene **122a** reacts with *m*CPBA to give the epoxy bridgehead lactone **151**.^[56] Lactone cleavage triggers rupture of the C–O epoxide bond to give the *cis*-hydroxydecalone derivative **152**, which under the reaction conditions lactonizes to tricyclic ketone **153**. The configuration at C-3, -4, and -5 is established during the cycloaddition step, while that at C-2 is established during the epoxidation of the bridgehead double bond.

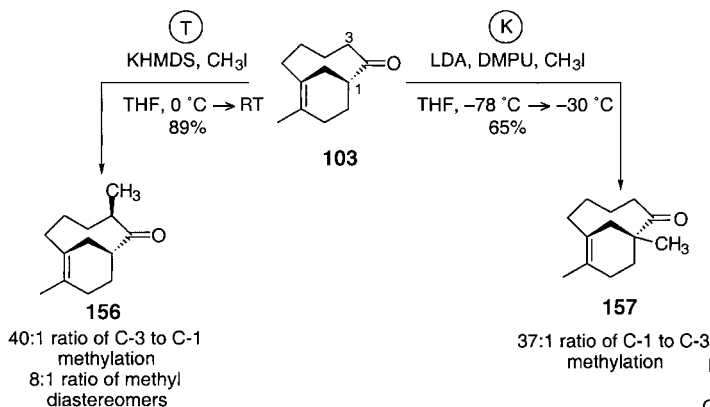
7.5.2. Functionalization of the Bicyclo[*n*.3.1] Ring System

Bridged bicyclic rings often have a well-defined conformational minima. As a result, the medium ring embedded in the [*n*.3.1] bridged bicycle can be stereoselectively elaborated. In general, stereocontrolled additions to the medium ring of the bridged bicycle occur from the *exo* face. This level of stereochemical control is often difficult to achieve with the monocyclic medium ring.^[68] The hydride reductions of ketones **19** and **28** demonstrate this principle (Scheme 20).^[50] The reduction with DIBALH at low temperature provides alcohols **154** and **155**, respectively, with high levels of diastereoselectivity.



Scheme 20. Stereoselective reduction of bicyclo[*n*.3.1] ketones to give alcohols. DIBALH = diisobutylaluminum hydride.

An interesting example of the control offered by a bridgehead alkene was in the alkylation of ketone **103** (Scheme 21).^[69] In contrast to aliphatic ketones, deprotonation of bicyclo[5.3.1]undecenone **103** gives the more highly

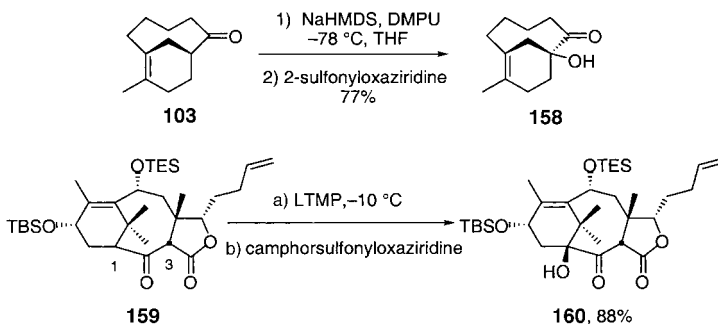


Scheme 21. Kinetic (K) versus thermodynamic control (T) in the alkylation of ketone **103**. KHMDS = potassium salt of hexamethyldisilazane, DMPU = 1,3-dimethylhexahydro-2-pyrimidinone.

substituted bridgehead enolate under conditions of kinetic control, while the less substituted enolate is formed under conditions of thermodynamic control. The origin of this unusual selectivity is understood by consideration of both strain and stereoelectronic factors. The C-1 carbon–hydrogen bond is aligned with the carbonyl π system, while the C-3 protons bisect the carbonyl π system. Thus, under *kinetic* control, deprotonation occurs more rapidly at C-1, resulting in preferential alkylation at the bridgehead carbon (>37:1). In

contrast, under conditions of thermodynamic control, the enolate with lower strain energy (C-2,C-3 double bond) is favored. As a consequence, methylation of ketone **103** under thermodynamic conditions gave exclusive (>40:1) C-3 alkylation consisting of an 8:1 ratio of diastereomers. The major diastereomer arises from *exo* addition of the methyl group.

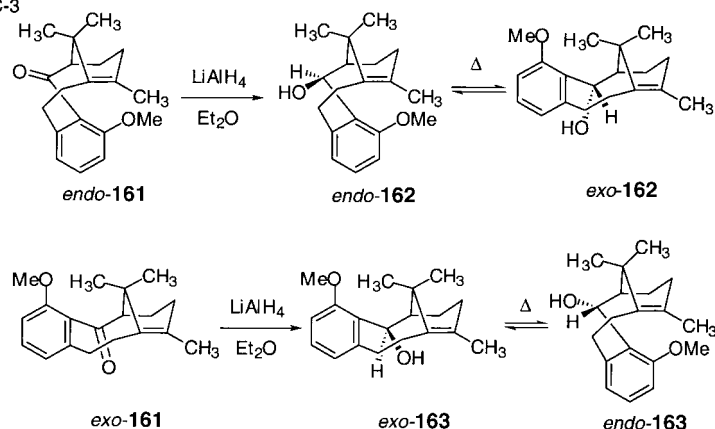
The bicyclo[5.3.1]undecene ring system is a key substructural feature of the taxane natural products. Bridgehead enolization/hydroxylation has been demonstrated on the parent bicyclo[5.3.1] ketone (**103** $\rightarrow$ **158**; Scheme 22).^[69] A



Scheme 22. Bridgehead hydroxylations of the bicyclo[5.3.1]undecenone ring system. TES = triethylsilyl, TBS = tributylsilyl, LTMP = lithium tetramethylpiperide.

related example of bridgehead functionalization (**159** $\rightarrow$ **160**) in the bicyclo[5.3.1] ring system was reported by Holton et al. in his Taxol synthesis.^[70] Deprotonation of **159** occurs at the bridgehead position even though the C-3 proton is expected to be more acidic. Others have also used this transformation for installation of the C-1 hydroxy group of taxane intermediates.^[71–73]

Other examples of stereoselective elaboration of medium-sized rings of bridged bicycles are found in the chemistry of a family of atropisomeric C-aromatic taxane derivatives. The type 2 IMDA reaction provided separable diastereomeric atropisomers of the tricyclo[9.3.1.0^{3,8}]pentadecane ring system.^[74, 75] The conformationally locked derivatives allowed a study of the effect of conformation on reaction stereochemistry (Scheme 23). Compounds *endo*-**161** and *exo*-**161** were

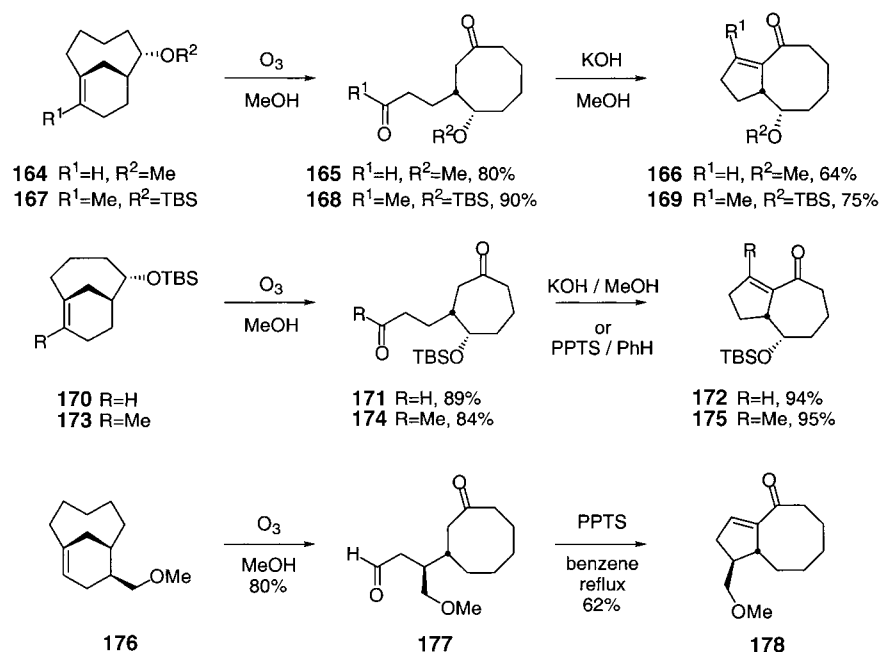


Scheme 23. Selective hydride reductions of atropisomers *endo*-**161** and *exo*-**161**.

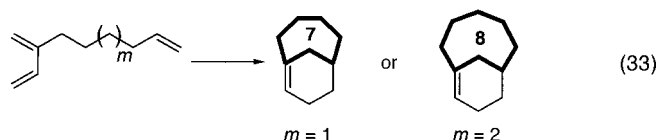
selectively reduced with lithium aluminum hydride to afford the corresponding alcohols, *endo*-**162** and *exo*-**163**, respectively. The kinetic reduction products could be thermally equilibrated, *endo*-**162** and *exo*-**163**, with their corresponding atropisomeric counterparts, *exo*-**162** and *endo*-**163**.

7.6. Synthesis of Medium-Sized Rings

The most successful type 2 IMDA reactions contain four or five atoms in the tether [Eq. (33)]. These cycloadditions give rise to cycloadducts with seven- or eight-membered rings embedded in the bridged bicyclic skeleton. The medium-sized rings can be prepared in a single step from acyclic precursors. The constrained rings can then be stereoselectively elaborated. Finally, oxidative cleav-



Scheme 24. Examples for bridged to fused ring interchange. PPTS = pyridinium *para*-toluenesulfonate.

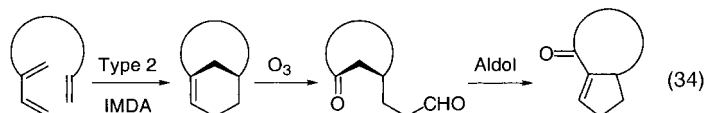


age of the bridgehead alkene releases the medium-sized ring for further modification.

An alternative strategy for the synthesis of medium-sized rings relies on addition to the bridgehead double bond followed by ring expansion. Examples of both strategies are described in the following sections.

7.6.1. Bridged to Fused Ring Interchange

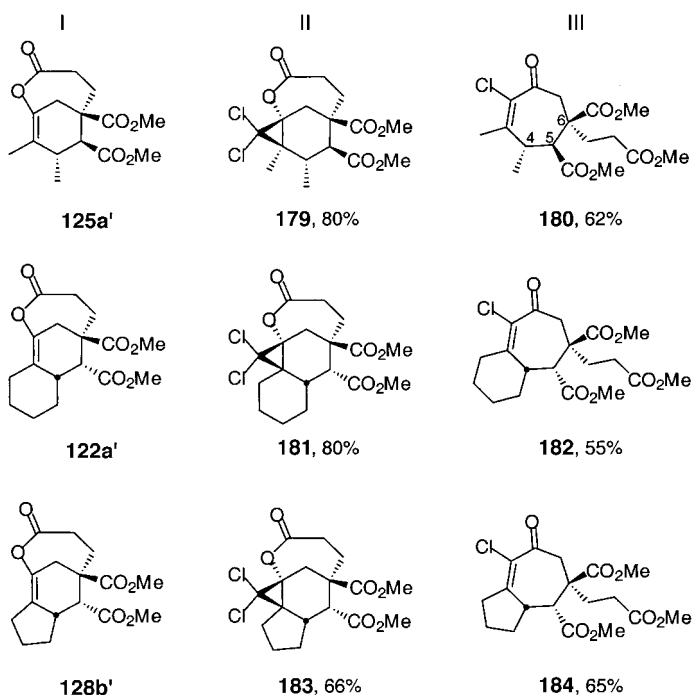
Oxidative cleavage of the bridgehead alkene liberates the medium-sized (seven- or eight-membered) ring. The resulting 1,6-dicarbonyl compound can subsequently be converted into a fused ring system with five and seven or five and eight ring atoms via an aldol cyclization [Eq. (34)]. The overall process has been referred to as bridged to fused ring interchange.



The reactions in Scheme 24 illustrate this concept.^[50, 76, 77] Following cycloaddition, ozonolysis of the bridgehead double bonds proceeds in high yield to liberate medium-sized ring dicarbonyl compounds which are condensed (under basic or acidic conditions) to form fused cycloheptane and cyclooctane ring systems. This methodology has been exploited in several natural product syntheses (see Section 8).

7.6.2. Ring Expansion of Bridgehead Alkenes

An alternative strategy for the synthesis of medium-sized rings by an addition–ring expansion strategy was developed for the stereospecific synthesis of substituted seven-membered rings (Scheme 25).^[78] The *exo* addition of dichlorocarbene (PhHgCBrCl_2 , PhH, reflux) to bridgehead enol lactones **125a'**, **122a'**, and **128b'** produces bridgehead dichlorocyclopropanes **179**, **181**, and **183**, respectively. Under basic conditions (MeOH , Na_2CO_3) the lactone is cleaved. The inter-



Scheme 25. Ring expansion in bridgehead enol lactones (I) to cycloheptenones (III) via cyclopropane intermediates (II).

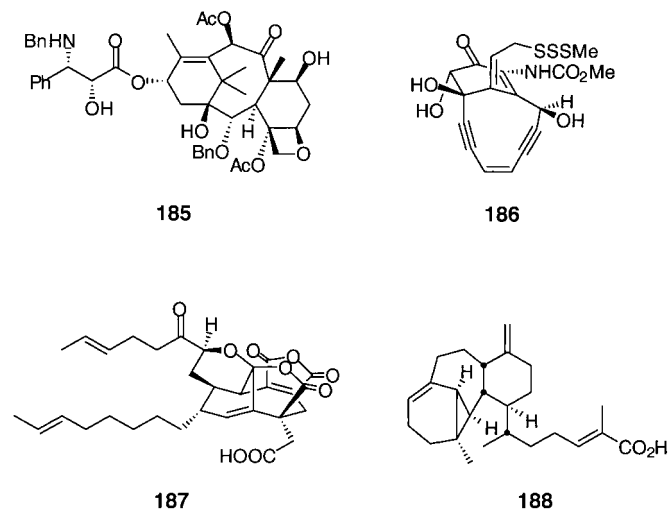
mediate dichlorocyclopropanol undergoes internal C–C bond cleavage with concomitant expulsion of chloride ion resulting in the formation of cycloheptenones **180**, **182**, and **184**, respectively. The cleavage of the internal C–C bond provides a stereoselective route to seven-membered chloroenones. The relative configuration of stereocenters 4, 5, and 6 are established in the cycloaddition step.

8. Applications in Natural Product Synthesis

The assembly of a bridged bicyclic skeleton in a single step from an acyclic precursor is a powerful synthetic tool. The direct application of this reaction as a key step in the synthesis of naturally occurring bridged bicyclic compounds is a confirmation of its practical utility. In addition to direct methods for the construction of naturally occurring bridged bicyclic rings, the regio- and stereocontrol of the type 2 IMDA has also been exploited in the synthesis of a number of natural products (i.e. adrenosterone, a *Plocamium* monoterpene, and ledol). Examples of both applications are given in the sections below.

8.1. Direct Applications

A number of biologically important natural products contain bridged bicyclic rings. Representative examples are the Taxol (**185**),^[79] esperamicin A₁ aglycone (**186**),^[80] CP-263,114 (**187**),^[81] and cerorubic acid (**188**)^[82] families of natural products (Scheme 26). The synthesis of advanced



Scheme 26. Representative examples of complex natural products with bridgehead double bonds.

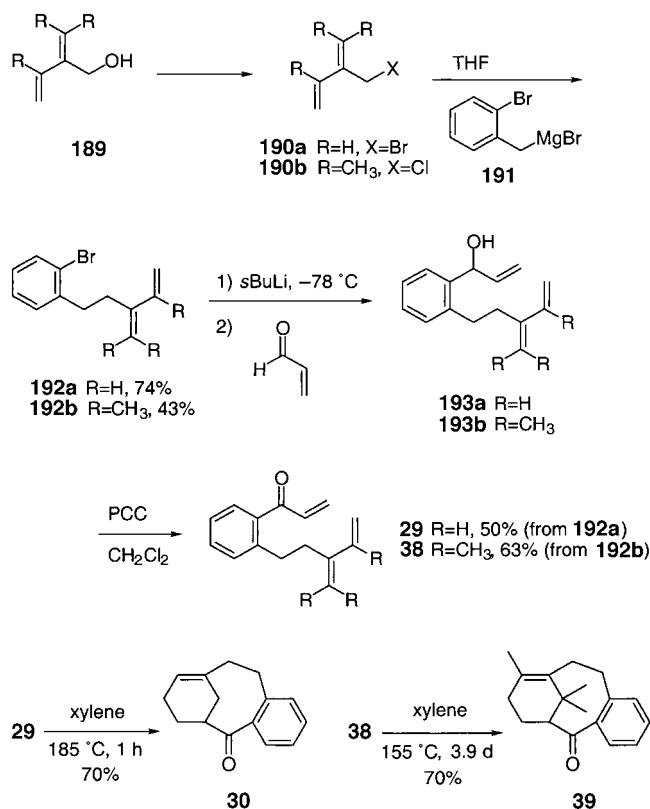
analogues of **185** and **186**^[83] and the total synthesis of **187**^[84] have used the type 2 IMDA reaction as the key step in the construction of the bridged bicyclic skeleton.

8.1.1. Taxanes

Taxol, the most celebrated member of the taxane family of natural products, was approved for the treatment of ovarian

cancer in 1992.^[79, 85] Prior to solving the problem of limited availability, there was an enormous synthetic effort toward the total synthesis of Taxol.^[79] Embedded in its complex structural core is a bridged tricyclo[9.3.1.0^{3,8}]pentadecene ring system with 11 stereocenters and a variety of differentially protected oxygen substituents.

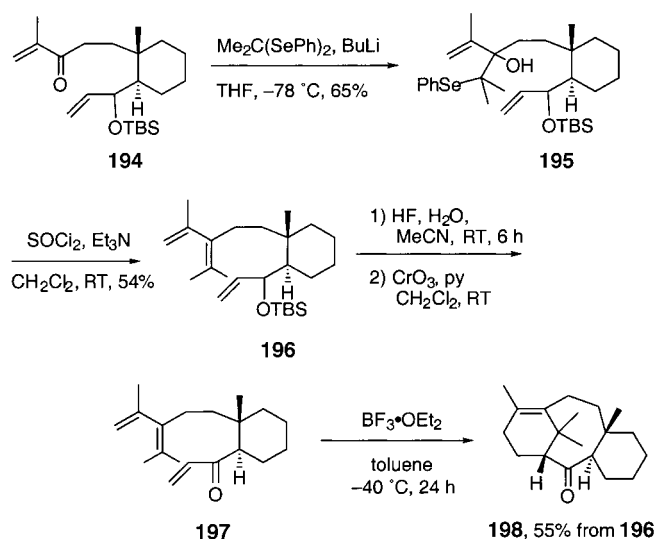
The type 2 IMDA reaction was employed in one of the first entries into this natural product, a C-aromatic taxane skeleton.^[38] Cycloaddition precursors **29** and **38** were synthesized by reaction of Grignard reagent **191**, prepared directly from the dibromide, with butadiene derivatives **190a** and **190b**, respectively (Scheme 27). The dienophile moiety of **29**



Scheme 27. Our synthesis of the C-aromatic taxane cores **30** and **39**.

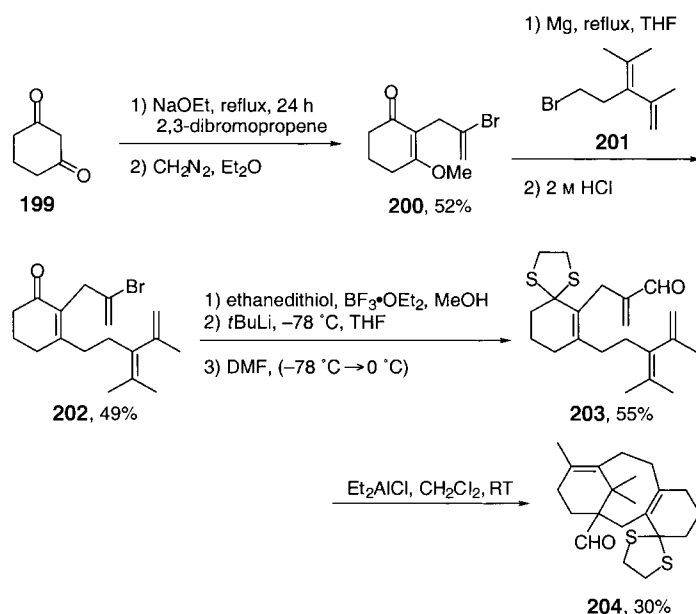
and **38** was introduced in two steps from **192a, b**. Metalation followed by addition of acrolein afforded alcohols **193a, b**, which upon oxidation yielded trienones **29** and **38**. Diels–Alder precursor **29** underwent thermally induced type 2 intramolecular Diels–Alder reaction to produce tricycle **30**. A particular concern in the application of this methodology to the taxane ring system was the use of a methylated diene. These concerns were assuaged with the successful cycloaddition of **38** in xylenes at 155 °C to produce the fully methylated A ring of taxane derivative **39**.

Jenkins and Bonnert were able to assemble the taxane core with the C-19 methyl substituent and the natural stereochemistry at C-1 and C-8 in a bridged-fused taxane tricycle containing a saturated C-ring (Scheme 28).^[86] The synthesis of triene **197** used an alternative route to the 2-substituted diene. A selenide reagent was used to introduce the geminal methyl groups at C-17 and C-18 (taxane numbering) of the diene

Scheme 28. Synthesis of taxane core **198** according to Jenkins and Bonnett.

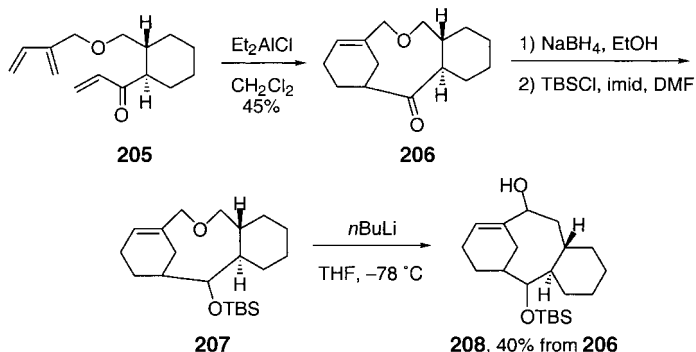
moiety. The synthesis involved the addition of $\text{LiCMe}_2\text{SePh}$ to enone **194** to produce hydroxy selenide **195**. Thionyl chloride assisted elimination of hydroxy selenide **195** gave desired triene **196**, which was deprotected and oxidized to give enone **197**. Treatment of **197** with a Lewis acid catalyst brought about the intramolecular Diels–Alder reaction to yield the taxane derivative **198**.

A related approach for the synthesis of an unsaturated C-ring analogue involved an internally activated dienophile (Scheme 29). Cycloaddition precursor **203** was prepared from 1,3-cyclohexadione (**199**).^[87] Alkylation with 2,3-dibromopropene followed by conversion to the vinylogous ester provided compound **200**. Treatment of **200** with the Grignard reagent of diene **201** followed by hydrolysis provided vinyl bromide **202**. Protection of the ketone and formylation of the vinyl bromide

Scheme 29. Our synthesis of saturated C-ring taxane core **204**.

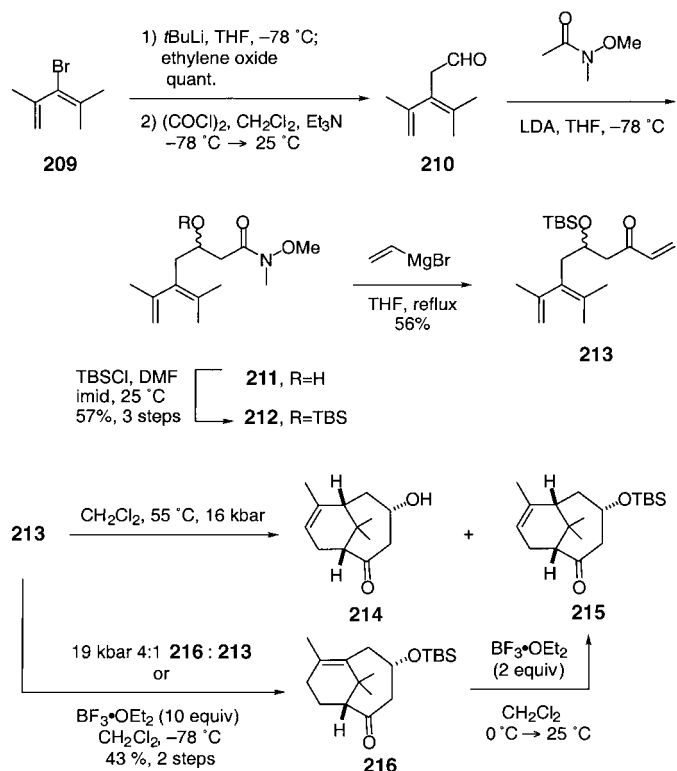
gave cycloaddition precursor **203**. Lewis acid catalyzed cyclization of **203** produced the taxane dithiane derivative **204**. The latent α,β -unsaturation in the C-ring was designed to serve as a handle for incorporation of the C-18 methyl group.

Yadav and Ravishankar used a combination of the type 2 IMDA reaction and a Wittig rearrangement to construct the taxane core (Scheme 30).^[88] Lewis acid catalyzed cycloaddi-

Scheme 30. Synthesis of taxane core **208** according to Yadav and Ravishankar. imid. = imidazole.

tion of enone **205** gave tricyclic adduct **206**. Reduction of the carbonyl group of **206** and protection of the resultant alcohol provided silyl ether **207**. Wittig rearrangement of ether **207** produced taxane core **208**.

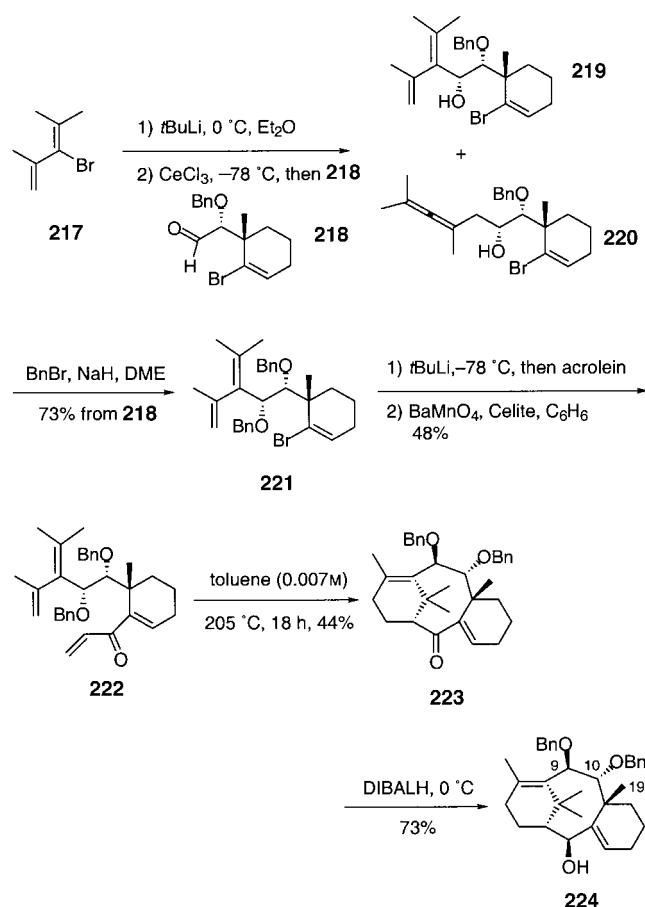
During the development of an intramolecular Diels–Alder ring-expansion approach to taxinine, Phillips and Abell were able to construct a bicyclo[4.2.1] ring system under conditions of high pressure (Scheme 31). Synthesis of cycloaddition



Scheme 31. Phillips and Abell's high-pressure type 2 IMDA reactions.

precursor **213** was initiated with the conversion of bromide **209** to the vinyl lithium species.^[89] Addition of ethylene oxide gave the alcohol, which was oxidized to aldehyde **210** under Swern conditions. Introduction of the Weinreb amide moiety by aldol addition gave alcohol **211**. Protection of alcohol **211** followed by Grignard addition produced enone **213**. Subjecting **213** to high pressure (16 kbar) resulted in the formation of cycloadducts **214** and **215**, products arising from cycloaddition followed by double bond isomerization. Higher pressure (19 kbar) provided a 4:1 ratio of bridgehead alkene **216** to enone **213**. Alternatively, treatment of enone **213** with excess $\text{BF}_3 \cdot \text{OEt}_2$ also gave type 2 IMDA product **216**, which could also be reacted further to give **215**.

Efforts to incorporate functionality at C-9 and C-10 and the pivotal C-19 angular methyl group have been addressed by several groups. One example was a thermally induced type 2 intramolecular Diels–Alder reaction of dienone **222** (Scheme 32).^[90] The synthesis of **222** started from aldehyde

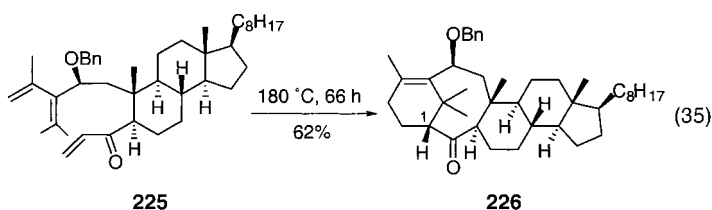


Scheme 32. Our synthesis of the functionalized taxane core **224**. DME = dimethoxyethane, Bn = benzyl.

218 which was treated with the cerium reagent derived from bromodiene **217** to produce a 4:1 mixture of diene alcohol **219** and allenyl alcohol **220**. Benzyl protection of the alcohols allowed isolation of bisbenzyl ether **221**. Metal–halogen exchange of bromide **221** followed by treatment with acrolein afforded a mixture of secondary alcohols, which were subsequently oxidized to enone **222**. Intermediate **222** underwent thermally induced cyclization to produce tricyclic cycloadduct **223**,

which was reduced to alcohol **224**. The structure of **224**, which was established by X-ray crystallography, revealed the cycloaddition of triene **222** afforded the C-1 *epi*-taxinine cycloadduct **223**. The reversal in π -facial selectivity was attributed to the unsaturation at C-3 and C-4 in Diels–Alder precursor **222**. Although the cycloaddition gave the incorrect relative stereochemistry at C-1, the reaction achieved the taxusin pattern of oxygenation at C-9 and C-10.

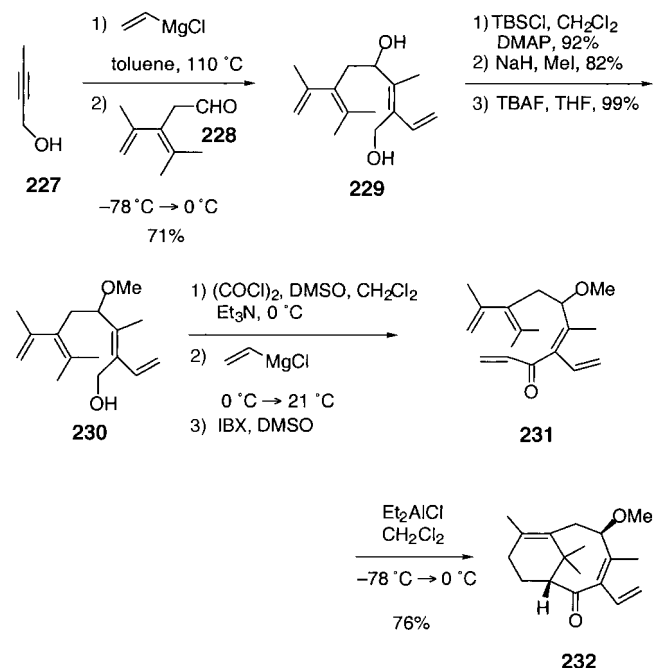
In efforts to explore the effects of substituents at C-9 and C-10 on the π -facial selectivity of the Diels–Alder reaction, Park et al. used a steroid-platform on which to perform the type 2 IMDA cycloaddition.^[91] This work resulted in a successful intramolecular Diels–Alder reaction leading to a Baccatin III-steroid hybrid [Eq. (35)]. Thermally induced



cyclization of **225** provided ketone **226**, which has the natural (C-1- β) configuration. Under the reaction conditions, elimination of the allylic alcohol at C-10 was found to compete with the cycloaddition.

Recently advanced taxusin intermediate **76** was synthesized by the type 2 IMDA reaction (see Scheme 7).^[32] In addition to the fully methylated taxane core, cycloadduct **76** contains the natural relative configurations about C-1, C-3, C-8, C-9, and C-10.

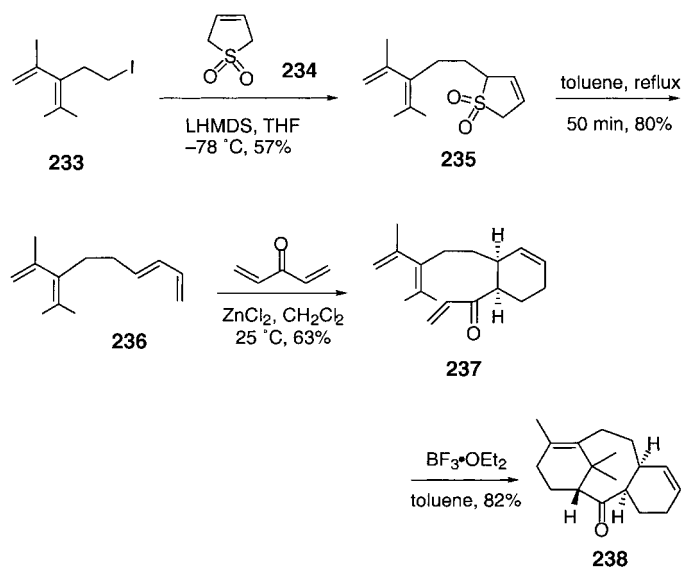
Fallis et al. were able to construct the AB rings of the taxane system using the type 2 IMDA reaction as the key step (Scheme 33).^[92] This synthesis began with the addition of



Scheme 33. Synthesis of taxane bicycle **232** according to Fallis et al. IBX = 1-hydroxy-1,2-benziodoxol-3(1H)-one-1-oxide (or *o*-iodoxybenzoic acid).

vinylmagnesium chloride to 2-butyne (**227**). The resultant magnesium complex was treated with aldehyde **228** to afford the tetraenediol **229**. The secondary alcohol was protected selectively as its methyl ether in three steps to give allylic ether **230**. Swern oxidation followed by vinyl Grignard addition and oxidation provided Diels–Alder precursor **231**. Subsequent Lewis acid catalyzed type 2 IMDA cycloaddition yielded the taxane core **232** as a single diastereomer. The origin of the diastereoselectivity arises from chelation of the Lewis acid to the methyl ether and carbonyl oxygen atoms during cycloaddition.

Winkler and co-workers have developed a tandem Diels–Alder approach to the taxane core (Scheme 34).^[93, 94] Reaction of the monoanion of the sulfone **234** with iodide **233**

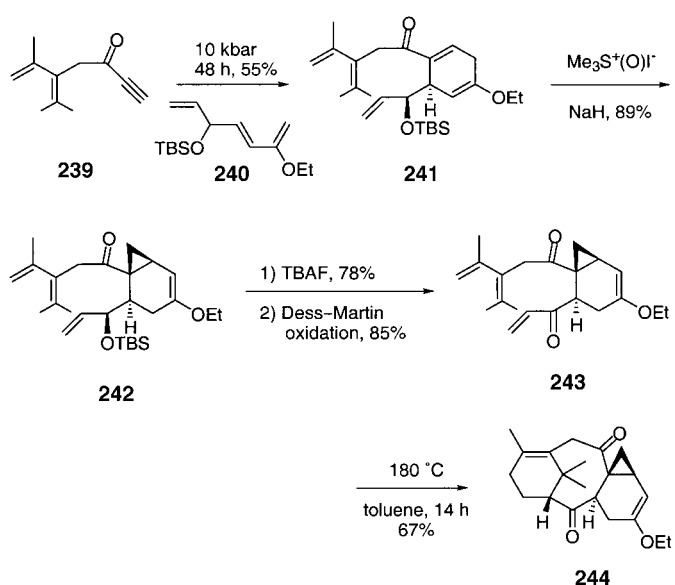


Scheme 34. Synthesis of taxane core **238** according to Winkler et al.

produced sulfone **235**. Extrusion of SO₂ from **235** (see Section 3.2.1) resulted in the formation of tetraene **236**. The choice of Lewis acid was important to stage the sequential Diels–Alder reactions (**236** → **238**). The C-ring was formed in a ZnCl₂-catalyzed intermolecular Diels–Alder reaction. This was followed by formation of the A-ring using BF₃·OEt₂. Although the core has limited substitution, this strategy provided a rapid entry into the tricyclic taxane framework. The synthesis plays upon the inherent reactivity of the two sets of dienes in tetraene **236**, where the difference in reactivity of the dienes allows the stepwise cycloadditions. Interestingly, neither Lewis acid was capable of catalyzing both Diels–Alder reactions in a one-pot transformation.

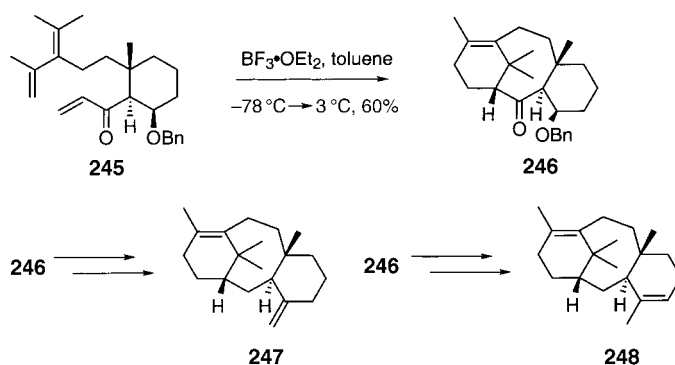
Winkler et al. were able to use a variation of the tandem Diels–Alder methodology to synthesize cyclopropyl taxane derivative **244** (Scheme 35).^[95] Cycloaddition of alkyne **239** and triene **240** led to the formation of 1,4-cyclohexadiene **241**. Cyclopropanation of enone **241** with concomitant $\Delta^{4,5}$ alkene migration provided bicycle **242**. Desilylation and oxidation provided intramolecular Diels–Alder substrate **243**, which upon heating gave tetracycle **244**.

The type 2 IMDA methodology has also been employed for the construction of related compounds in the taxoid family.



Scheme 35. Synthesis of cyclopropyl taxane derivative **244** according to Winkler et al.

Williams and Rubenstein reported the synthesis of putative biosynthetic Taxol intermediates taxa-4(20), 11-diene **247** and taxa-4, 11-diene **248** (Scheme 36).^[96] Lewis acid catalyzed type 2 IMDA cyclization provided tricyclic compound **246**, which was elaborated to both **247** and **248**.

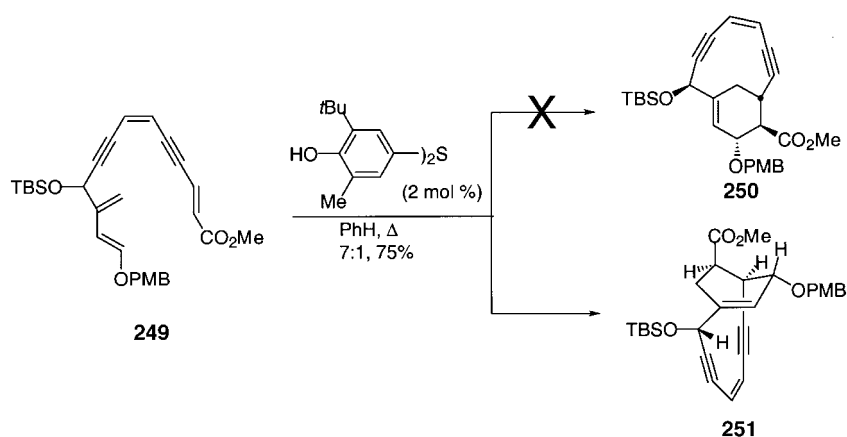


Scheme 36. Synthesis of Taxol biosynthetic intermediates **247** and **248** according to Williams and Rubenstein.

8.1.2. Esperamicin

The esperamicin/calicheamicin core contains a bicyclo-[7.3.1]tridecanone bridged core (**186** in Scheme 26). Common to the esperamicin/calicheamicin natural products is the enediyne structural unit that imparts the unique biological activity of this class of antitumor agents. The enediyne unit is incorporated across the cyclohexene ring in a 1,3-disposition. This was recognized as a structural feature that could be synthesized by a type 2 IMDA reaction.

Entry into the esperamicin/calicheamicin core was first attempted by the type 2 IMDA reaction of enediyne **249** (Scheme 37).^[83] Inherent in the cycloaddition of compound **249** was the issue of the regiochemistry of the cycloaddition. The initial report concluded the cycloaddition of **249** afforded **250**. Interestingly, a reinvestigation of this reaction and the



Scheme 37. Type 2 IMDA cycloaddition of polyenyne **249**. PMB = *para*-methylbenzoyl.

products resulting from subsequent transformations of the putative cycloadduct revealed the original regiochemical assignment (*meta*) was incorrect, the product was reassigned to the *para* regioisomer **251**.^[83c]

With a somewhat revised synthetic plan, Schreiber et al. developed a strategy to isomerize the initially formed 1,4-regioisomer to the required 1,3-regioisomer of the esperamicin/calichemicin natural products (Scheme 38).^[83a] Diels–

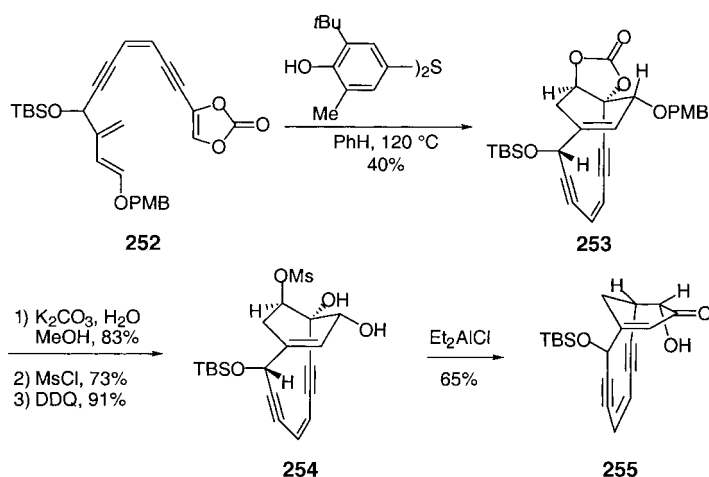
diethylaluminum chloride delivered the Tsuchihashi–pinacol adduct **255** in 65% yield. Confirmation of the structure was obtained by X-ray crystallographic analysis of a derivative of **255**.

This sequence of reactions demonstrates the range of sensitive functionality that can be successfully carried through the cycloaddition reaction.

8.1.3. CP-263,114 and CP-225,917

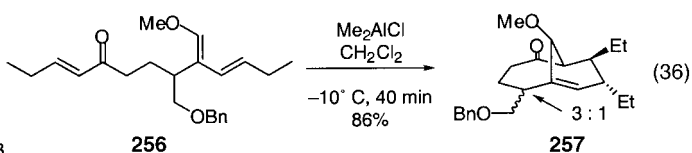
The CP family of natural products has received considerable attention based on their biological activity as leads for cholesterol-lowering and anticancer agents. The

core of the CP molecules consists of a bicyclo[4.3.1]decene ring system. A number of syntheses of this ring system employing the type 2 IMDA reaction had been reported earlier,^[4, 50] providing a strong precedent for its use in the CP series. Nicolaou et al. reported a synthesis of the bicyclic CP core starting from a type 2 IMDA reaction of triene **256** [Eq. (36)].^[97] Lewis acid induced cyclization of IMDA pre-



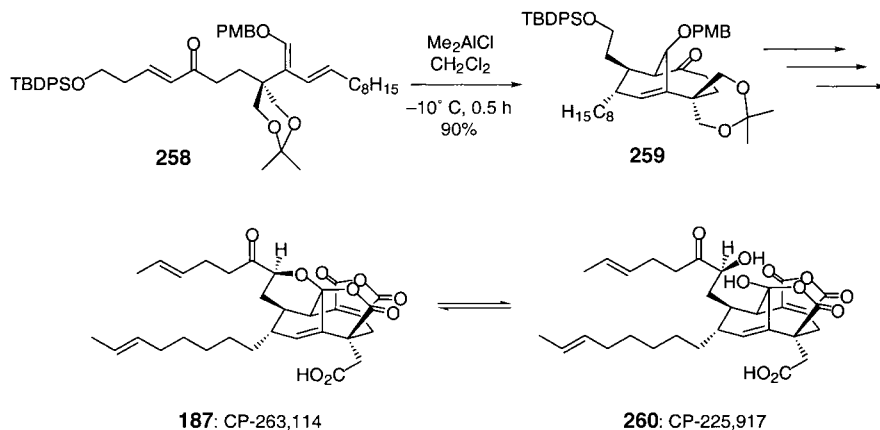
Scheme 38. Synthesis of esperamicin core **255** according to Schreiber et al. Ms = methanesulfonyl, DDQ = dichlorodicyanobenzoquinone.

Alder precursor **252** was heated in the presence of a radical inhibitor to induce the intramolecular cycloaddition that afforded 1,4-regioisomer **253**. Saponification of the carbonate followed by mesylation of the secondary alcohol and debenzoylation afforded the pinacol substrate **254**. The isomeric skeleton obtained from the cycloaddition was shown to undergo a Tsuchihashi–pinacol rearrangement with concomitant and diastereoselective acyloin shift to provide the natural ring system. Treatment of **254** with six equivalents of



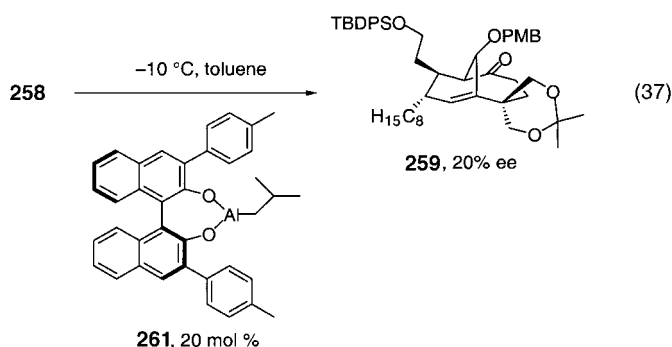
cursor **256** afforded ketone **257** as a mixture of diastereomers. The configuration of the major diastereomer was not determined.

Nicolaou and co-workers employed a more highly elaborated Diels–Alder precursor (**258**) in the total syntheses of racemic CP-225,917 (**260**) and CP-263,114 (**187**) (Scheme 39).^[84a,b] Lewis acid catalyzed intramolecular Diels–Alder cycloaddition of **258** provided bridged bicycle **259**. Following a series of functional group manipulations of the cycloadduct, bicycle **259** was converted to **187** and **260**. The Nicolaou group utilized this strategy for the development of an enantioselective synthesis of both CP compounds.^[98] A variety of chiral

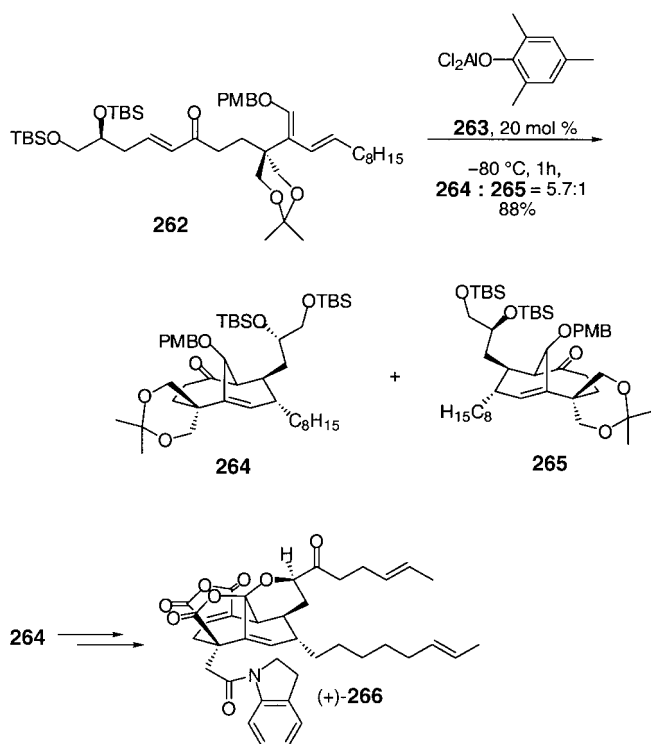


Scheme 39. Synthesis of CP molecules **187** and **260** according to Nicolaou et al.

Lewis acids were employed for the cycloaddition of prochiral ketone **258**. Catalyst screening identified the binol aluminum derivative **261** as the optimal inducer of asymmetry, although the best enantiomeric excess was a disappointing 20% [Eq. (37)].



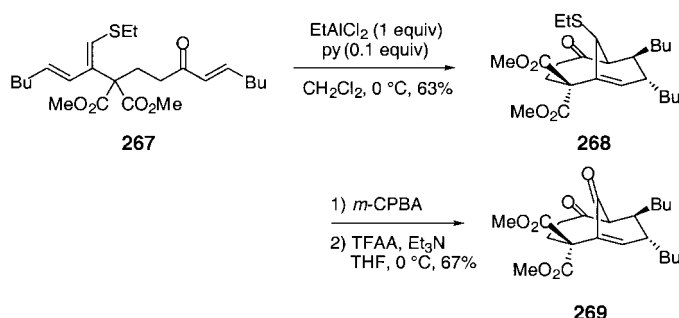
In efforts to determine the absolute configuration of the natural product, chiral precursor **262** was prepared from (*R*)-glycidol.^[98] Treatment of **262** with 20 mol % of catalyst **263** at -80°C in toluene led to a 5.7:1 mixture (70% *de*) of diastereomeric cycloadducts **264** and **265** in 88% yield (Scheme 40). Subsequent transformation of major diaster-



Scheme 40. Diastereoselective cycloaddition and determination of the absolute configuration of CP-263,114.

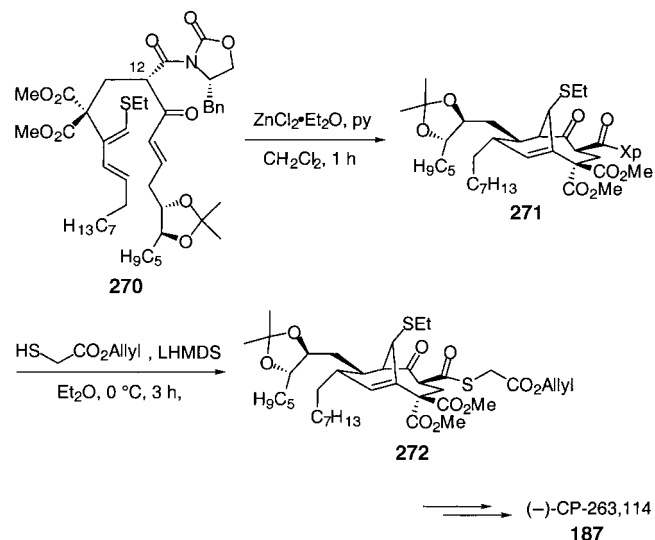
eomer **264** to (+)-**266** allowed direct comparison with (–)-**266**, prepared from a natural sample of (–)-CP-263,114. This sequence established the absolute configuration of (–)-CP-263,114 and (+)-CP-225,917. The synthetic product (+)-**266** was processed to give *ent*-**187** and *ent*-**260**, thus establishing an asymmetric route to the CP molecules.

Fukuyama et al. also reported the synthesis of the CP core by a type 2 IMDA reaction. In the initial report the synthesis of bicyclic ketone **269**, a molecule that possesses many of the functional groups and stereogenic centers required for the construction of CP-225,917 and CP-263,114, was described (Scheme 41).^[99] The core was synthesized by treatment of



Scheme 41. Synthesis of CP core **269** according to Fukuyama et al.

ketone **267** with EtAlCl_2 to give bridgehead alkene **268** in 63% yield. The structure of cycloadduct **268** was confirmed by X-ray crystallography. Elaboration of **268** to bicyclic diketone **269** was accomplished by sulfur oxidation followed by a Pummerer rearrangement. Fukuyama et al. subsequently reported the asymmetric total synthesis of (–)-CP-263,114 (**187**) in which they utilized a type 2 IMDA reaction to construct the bicyclo[4.3.1]decene ring system (Scheme 42).^[84c] Diastereoselective cycloaddition of IMDA pre-



Scheme 42. Synthesis of (–)-CP-263,114 (**187**) according to Fukuyama et al.

cursor **270** afforded cycloadduct **271** which was treated with lithium thiolate to produce thio ester **272** in 53% for the two steps. The diastereoselectivity of the cycloaddition is controlled by the C12 substituent.

The total syntheses of CP-263,114 and CP-225,917 were important synthetic achievements. The structural complexity contained within a small, compact natural product reveals the utility of type 2 IMDA methodology in natural product synthesis.

8.2. Indirect Applications of the Type 2 IMDA Reaction in Natural Product Synthesis: Utilization of the Stereochemical and Regiochemical Control Elements

The direct application of the type 2 IMDA reaction to construct the bicyclic cores of naturally occurring substances will continue to expand the importance of this reaction. Perhaps as important however, is the ability of this reaction to control the stereo- and regiochemistry of the Diels–Alder cycloaddition. The use of this strategy provides new paradigms for the analysis of synthetic problems and enhances the opportunity to draw upon the Diels–Alder reaction for the synthesis of complex natural product targets.

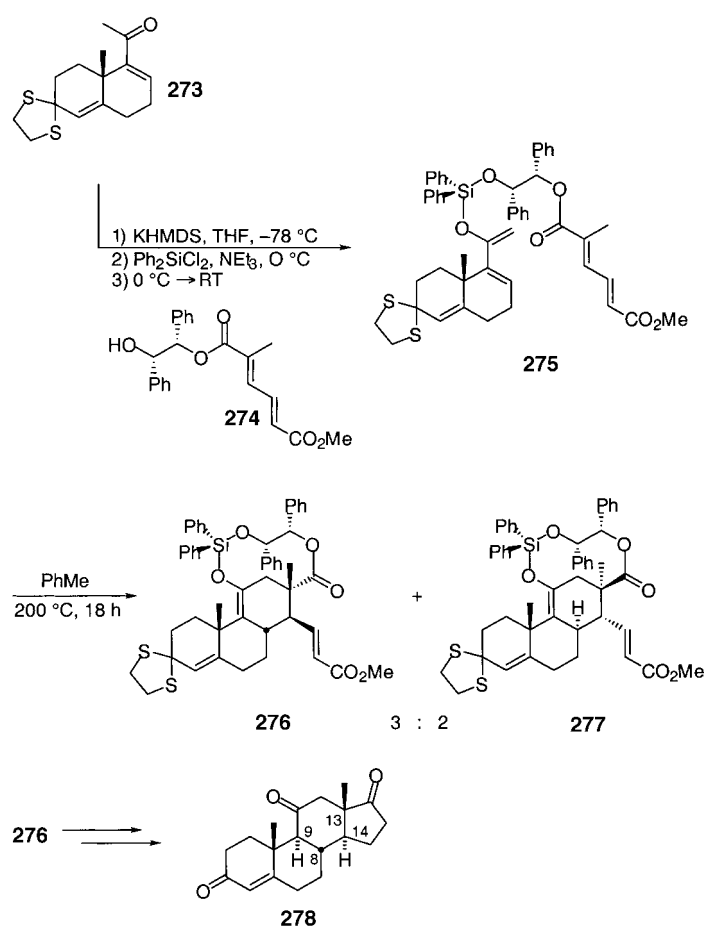
8.2.1. Disposable Tethers

The enantiospecific synthesis of the adrenalcorticosteroid (+)-adrenosterone was accomplished by using disposable tether methodology.^[100] Building upon the Wieland–Miescher ketone, it was envisioned that a type 2 IMDA reaction could be used to construct the C-ring and establish the four stereocenters in the BCD ring junctures (C-8, C-9, C-13, and C-14) of the steroid. This step required reversal of the “normal” regiochemical outcome of the bimolecular cycloaddition. This requirement was realized by using a type 2 IMDA reaction that employed a chiral disposable silaacetal tether uniting the diene and dienophile. Enone **273** was kinetically deprotonated, trapped as the (chlorodiphenyl)silyl dienyl ether, and quenched with (–)-hydrobenzoin ester **274** to give silaacetal **275** (Scheme 43). Silaacetal **275** was heated to 200 °C in toluene for 18 h, which provided a 3:2 mixture of **276:277** in 90% yield (based on **273**, 45% conversion). The major cycloadduct **276** arose from α -approach of the dienophile to provide the correct stereochemical relationship between the C-10 methyl and the stereocenters at the BCD ring junctures. Cycloadduct **276** was carried on to complete the synthesis of (+)-adrenosterone (**278**).

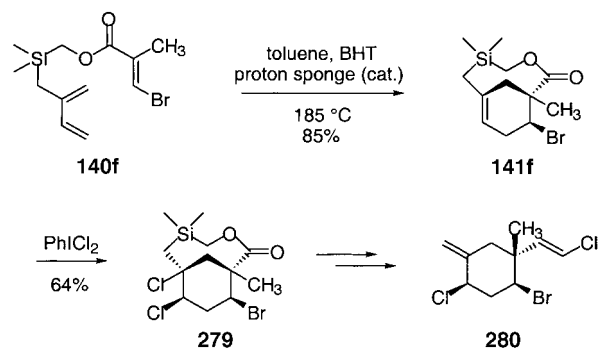
A variety of polyhalogenated monoterpene natural products have been isolated from the red marine algae *Plocamium* sp.^[101] The quaternary center and complex halogenation pattern of these compounds represent a significant synthetic challenge. Disposable tether methodology was employed in the total synthesis of *Plocamium* monoterpene natural product **280** (Scheme 44).^[102] The type 2 IMDA cycloaddition of **140f** provides complete regiochemical control to deliver cycloadduct **141f**. Bridgehead allylsilane **141f** was then *exo*-chlorinated with (dichloroiodo)benzene to give the polyhalogenated cyclohexane **279**. This intermediate was subsequently elaborated in three steps to the polyhalogenated *Plocamium* monoterpene natural product **280**.

8.2.2. An Application of Bridged to Fused Ring Interchange

The aromadendranes are a class of sesquiterpene natural products which are characterized by a dimethylcyclopropane unit fused to a hydroazulene core.^[103] Ledol is a representative of this class and shows antifungal activity against *Coriulus renatus*.^[104] The type 2 IMDA reaction has been shown to be an efficient method for the synthesis of medium rings. Setting

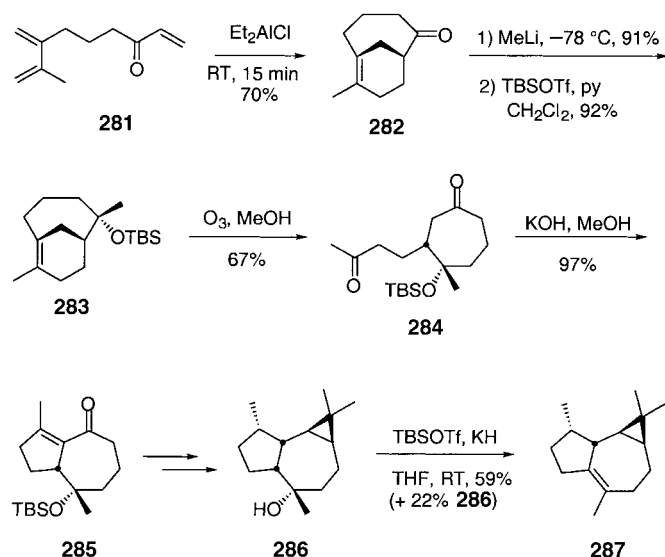


Scheme 43. Our enantioselective synthesis of (+)-adrenosterone (**278**).



Scheme 44. Our synthesis of *Plocamium* monoterpene **280**.

stereochemistry in medium rings can be difficult due to their conformational flexibility.^[68] An attractive feature of the type 2 IMDA methodology presented below is the stereochemistry of the medium ring can be set while taking advantage of the rigidity of the bicyclic intermediate. Capitalizing on this feature, we reported total syntheses of ledol and ledene.^[50, 77] The seven-membered ring in ledol was formed from the type 2 IMDA cycloaddition. The Lewis acid catalyzed type 2 IMDA cycloaddition of triene **281** proceeded to give bridged bicycle **282** in 70% yield (Scheme 45). Stereoselective functional group manipulation of the bicyclo[*n*.3.1] ring system followed to establish the relative stereochemistry. Treatment of ketone **282** with MeLi afforded



Scheme 45. Our synthesis of ledol (286) and ledene (287).

the corresponding alcohol with complete stereoselection in 91% yield. After protection of the alcohol, the resulting bridgehead alkene **283** was subjected to bridged to fused ring interchange. This is accomplished first by ozonolysis to afford dicarbonyl **284** and then aldol cyclization to produce the fused ring system **285** required for the synthesis of ledol (**286**). Subsequently, ledol was successfully dehydrated to ledene (**287**).

9. Summary and Outlook

In a relatively short time, anti-Bredt alkenes have evolved from a class of chemical oddities to species that play a key role in the synthesis of complex natural products. The type 2 IMDA reaction, a simple intramolecular variant of the venerable Diels–Alder cycloaddition, provides a direct route to this family of compounds in a single step from an acyclic precursor. The scope of the type 2 IMDA reaction is impressive. Products range from some of the most highly strained isolable anti-Bredt alkenes to the core of Taxol. The regiochemical and stereochemical bias of the intramolecular cycloaddition have produced strategies for selecting a single isomeric product from the Diels–Alder reaction. The utility of this innovation was broadened by the development of disposable tethers, temporary connectors of the diene and dienophile that capitalized on the reactions selectivity. In some cases, the regiochemistry of the type 2 IMDA cycloadduct is reversed from the bimolecular counterpart. This *pericyclic umpolung* creates new strategies for planning organic syntheses. In more recent developments, the type 2 IMDA reaction has served a key step in the construction of complex polycyclic rings that make up the core of a number of important natural products. It is certain that the utilization of the type 2 IMDA reaction in organic synthesis will continue to grow. One important area for future development is the heteroatom variant of the reaction to afford direct synthetic entries into medium ring heterocycles. The regiochemical and

stereochemical control of the type 2 IMDA reaction is a particularly attractive feature of this approach.

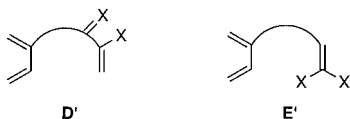
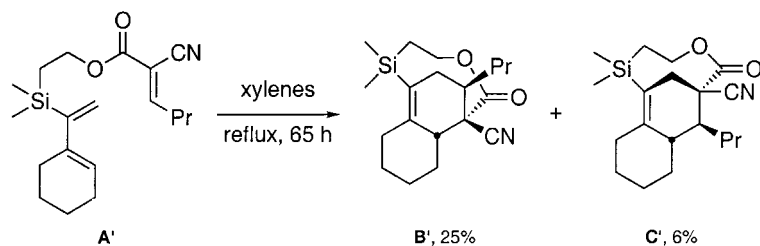
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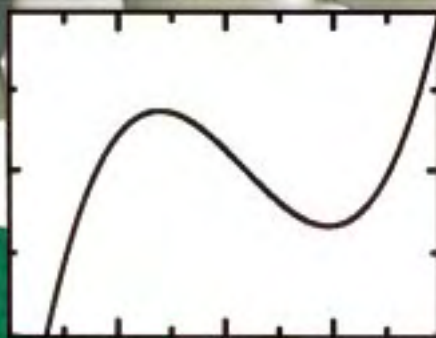
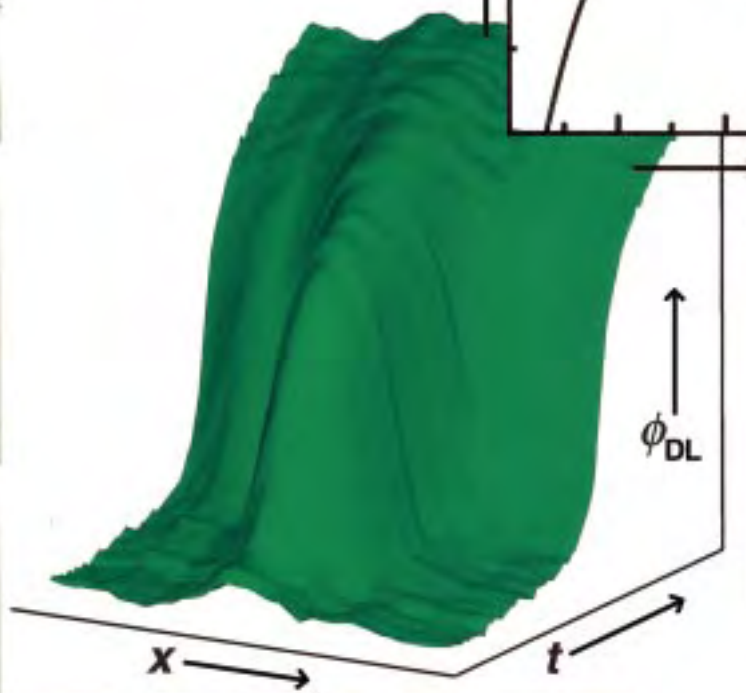
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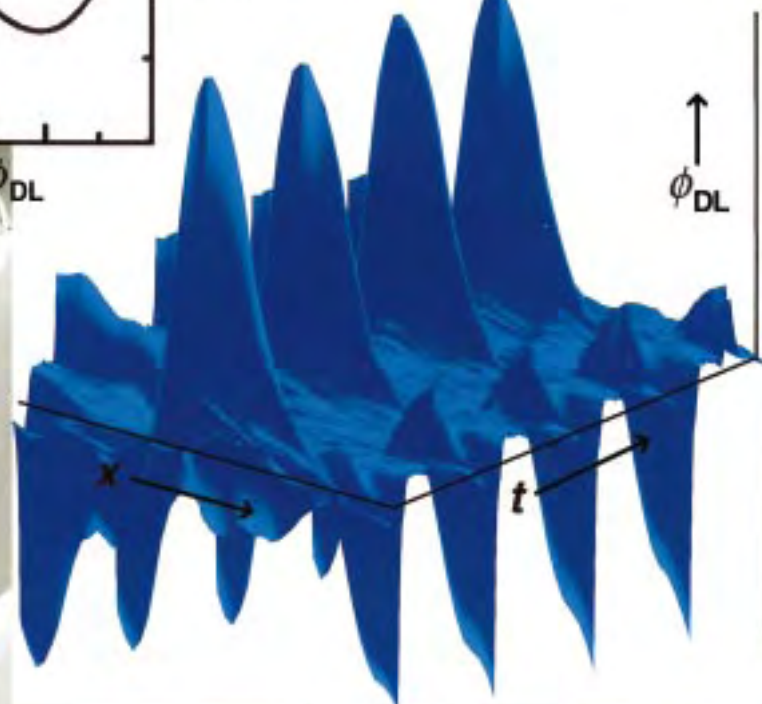


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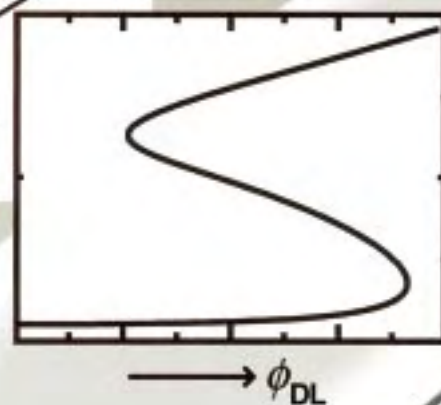
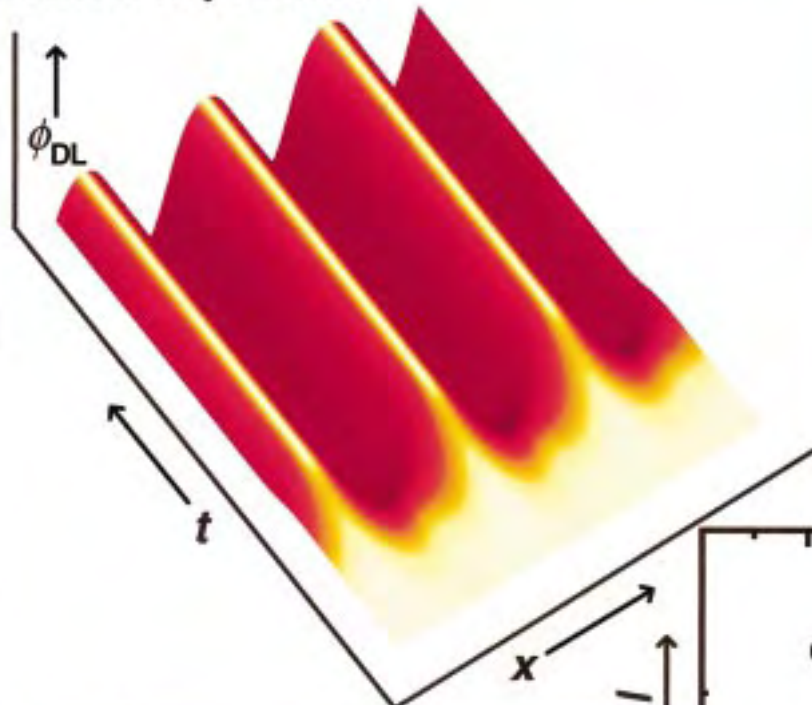
Fronts...



...Waves...



...Stationary Patterns



Fronts, Waves, and Stationary Patterns in Electrochemical Systems**

Katharina Krischer,* Nadia Mazouz, and Peter Grauel

Oscillatory behavior has been observed for almost all electrochemical reactions in a certain, although sometimes small, range of external parameters. Only in the past ten years has it been possible, however, to find a common explanation for the occurrence of these temporal self-organization phenomena of chemically completely different electrochemical reactions. The breakthrough was achieved because new methods and concepts, which had been developed in nonlinear dynamics to describe the spontaneous formation of order in various disciplines, could be applied. This development in turn was only possible because

the underlying laws are universal at a certain abstract level. Oscillations are only one possible manifestation of nonlinear behavior. Examples of other features that are often closely associated with temporal instabilities are spatial structures and waves. Initiated by the theoretical progress and the development of new experimental techniques, spatial pattern formation in electrochemical systems has been targeted for investigations in the past few years. Based on these investigations, it can be predicted under which conditions temporal or spatial pattern formation can be expected. Furthermore, the possibility of predicting the

occurrence of instabilities indicates that it might be feasible to exploit nonlinear effects to increase, for example, the yield of electrocatalytic reactions. Here we discuss physicochemical mechanisms that lead to pattern formation in electrochemical systems. At the same time, we stress the generic principles that are responsible for self-structuring processes in many chemical and biological systems.

Keywords: autocatalysis • electrochemistry • nonlinear dynamics • pattern formation • self-organization

1. Introduction

I would like to hold off on any comment on my beliefs about the cause of these strange appearances until an experimental basis can be offered to you.^[1]

Wilhelm Ostwald, 1900

A system far from thermodynamic equilibrium can spontaneously form a state of higher order if the evolution equations of the system are nonlinear and fulfill certain requirements.^[2] This knowledge led to a new understanding of many natural phenomena in the second half of the 20th century. For example, a metal wire that spontaneously forms a hot and a cold zone cannot be explained in classical thermodynamics. However, this very phenomenon can be observed when the wire catalyzes a chemical reaction and the average temper-

ature of the wire is kept constant.^[3, 4] As a result of the composition of the reactants and the control of the temperature the system is far from equilibrium. The evolution equations for the local temperature and the local activity of the wire contain appropriate terms. Both the nonequilibrium condition and the nonlinear evolution equation enable an export of entropy out of the system, and results in a state of higher order within the system. A process that results in a state of higher order in a system by exporting entropy out of it is called a self-organization process. Examples of self-organization can be found in all the natural sciences. Conditions under which order can develop on mesoscopic and macroscopic scales are at the center of nonlinear dynamics.

One of the main findings of the theory of nonlinear systems is that complex motion or structures can originate from the interaction of a few variables rather than through the linear superposition of many degrees of freedom. In this context, the occurrence of deterministic chaos is certainly the most spectacular feature. It is also responsible for the limited predictability of the dynamics of macroscopic systems. Furthermore, results from various scientific disciplines have shown that mechanisms leading to the occurrence of nonequilibrium structures are universal. The same fundamental laws are responsible for the periodic rhythms in "chemical

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[**] In the appendix we list the minimal equations (prototype equations) that describe the phenomena of self-organization discussed in the individual sections.

clocks", many biological systems, some semiconductors and lasers, and the electrochemical systems described here. Thus, this overview of electrochemical self-organization can be looked at from an interdisciplinary point of view as well. On a certain abstract level, the basic principles can be applied to many systems that are fundamentally different in nature, especially to chemical pattern-forming systems.

If we look at the mechanism that results in instabilities from the point of view of physical chemistry, it is already clear by glancing at the history of chemical oscillations that electrochemical reactions need to have a special feature that favors the occurrence of instabilities. The first electrochemical oscillations were described in the 1820s, more than 100 years before those of other chemical systems.^[5] Today, the number of known electrochemical systems displaying self-organization is greater by far than that of chemical oscillators in homogeneous phases (many have been listed in review articles^[6–8]).

The most famous example is the electrooxidation of metals, above all, that of iron, which has been investigated as a chemical model for nerve impulse propagation at the beginning of the 20th century.^[9, 10] Deposition of metals is also often connected with oscillations of the reaction rate. The same applies to apparently simple oxidation and reduction reactions, such as the oxidation of Fe^{2+} , iodide, or hydrogen or the reduction of peroxodisulfate, iodate, or periodate. Furthermore, electrocatalytic reactions exhibit dynamic instabilities, which start with the oxidation of formic acid, formaldehyde, and methanol, continue with members of their respective homologous series, and end with the reduction of hydrogen peroxide and oxygen.

In contrast to chemical reactions performed in a homogeneous phase under isothermal conditions, almost all electrochemical reactions are observed to have oscillating behavior in a certain range of the external parameters (for example, voltage or bulk concentrations of the reactants). The frequent occurrences of phenomena of self-organization are widespread in electrochemical reactions, which explains the long history of these chemical oscillators. It also shows how important it is to understand the physicochemical origins of these occurrences in chemically completely different reactions. It has not yet been ten years since a general explanation, based on some previous research, was given for temporal instabilities of electrochemical oscillators.^[11] A general mathematical model for spatial pattern formation was formulated about five years ago.^[12] This gain in understanding led to a new wave of experimental investigations, which in turn brought to light a variety of spatiotemporal phenomena at the electrode/electrolyte interface.

As is the case for electrochemical pattern formation, chemical oscillators presented in this review can be described by so-called reaction–transport equations.^[13] The term “reaction” stands for the dynamic of the system in the absence of any spatial inhomogeneities, that is, for the homogeneous system. The “transport” term plays a role only when spatial variations are present in the variables parallel to the spatial domain, which in our case is the electrode.

As a necessary prerequisite for the formation of spatial patterns, the reaction part (that is, the homogeneous dynamic) has to have a certain structure that often results in temporal instabilities such as bistable or oscillatory behavior.^[14] Thus,

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spatiotemporal pattern formation in electrochemical systems. In 1998 she obtained her Habilitation from the FU, Berlin, and became a lecturer in Physical Chemistry. She was honored with the Otto Hahn Medal of the MPG, the ADUC annual award (ADUC Jahrespreis für Habilitanden), and the de Gruyters Award of the Berlin-Brandenburg Academy of Sciences. Her research interests include all overlapping aspects of electrochemistry and nonlinear dynamics.

Nadia Mazouz studied Physics and Philosophy in Berlin. Having obtained her Diplom in Physics from the Technical University (TU), Berlin, in 1996, she worked on theoretical studies of self-organization processes of electrode reactions at the Fritz-Haber-Institute, Berlin. She obtained her PhD on the same studies in 1999 from the FU, Berlin. Since then, aside from the theory of complex systems, her studies have intensified again on philosophical questions.

Peter Grauel graduated in Chemistry from the University of Frankfurt in 1995. He then worked on experimental studies of interfaces and studies of electrochemical structure formation processes at the Fritz-Haber-Institute, Berlin. He obtained his PhD from the FU Berlin in 1999, and has since been working as a scientific researcher at the Fritz-Haber-Institute.

spatial pattern formation is the result of the interaction of a homogeneous dynamic and lateral transport processes.

The transport process connected to pattern formation in chemical systems is essentially always diffusion. Chemical systems, especially the Belousov–Zhabotinsky reaction, are considered prototypes of pattern-forming systems and model systems for biological systems. Thus, most theoretical studies on pattern formation in reaction–transport systems concentrate on pattern formations in reaction–diffusion systems. As we will discuss, the dominant spatial coupling in electrochemical systems results from changes of the electric field in the electrolyte. This coupling differs from the diffusion coupling in some aspects, and can lead to qualitative new behavior in pattern formation.

This review gives an overview on the latest developments in electrochemical processes of self-organization. Section 2 covers systems whose behavior can be described by spatiotemporal changes in the double-layer potential alone, the central variable in electrochemistry. We will show that the double-layer potential behaves autocatalytically in these systems. We expand our presentation in Section 3 to situations where the dynamic behavior is influenced not only by an autocatalytic double-layer potential but also by an additional—chemical—variable, namely a concentration or a coverage of the electrode. The feedback of this additional variable onto the temporal development of the double-layer potential results in oscillating behavior that is the key characteristic of all features presented in this section. Subsection 3.1 deals with more complex forms of oscillations that are displayed when the system has an additional feedback loop. Finally, Section 4 describes systems in which the roles of the chemical variable and the double-layer potential are reversed with respect to those discussed in Section 3. Section 5 summarizes the characteristics of pattern formation in electrochemical systems and discusses future perspectives.

The three main Sections 2–4 have the same setup. First, the homogeneous system is presented, then the influence of transport processes parallel to the electrode is taken into account, and finally, the influence of an external control of the reaction on pattern formation is discussed. Such a control of the reaction could occur if the total current is kept constant, for example.

2. Fronts in Bistable Systems

The simplest nontrivial behavior of a nonlinear system is bistability, whereby two stable, stationary and spatially homogeneous states coexist in a certain range of the experimental parameters.^[14, 15] These states are stable with respect to sufficiently small perturbations. For larger perturbations, the system can show transitions from one state to the other. The transitions are normally not homogeneous, that is, they do not occur at all locations of the system at the same time. Rather, they are associated with the formation and propagation of fronts: narrow, propagating regions that connect the areas of the system that are in different states.

2.1. Homogeneous Dynamic

The occurrence of bistable behavior in electrochemical systems is closely associated with the operational mode of the experiment. A standard setup of an electrochemical experiment is shown in Figure 1a. Investigations focus on the interface

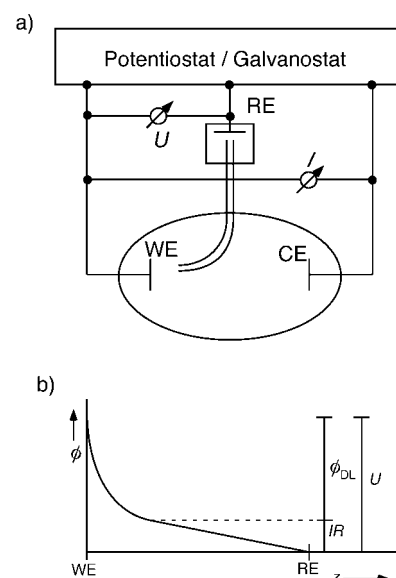


Figure 1. a) Basic electrochemical experimental setup. WE: working electrode, CE: counter electrode, RE: reference electrode. The reference electrode is in a separate compartment, and is connected to the actual electrochemical cell by an electrolyte bridge (Luggin capillary). b) Distribution of the voltage drop between the working electrode and the reference electrode in terms of the voltage drop across the double layer ϕ_{DL} and the Ohmic (IR) drop in the electrolyte. z is the spatial direction perpendicular to the electrode.

between the working electrode (WE) and an electrolyte. If a current flows through this interface, the second transition, from an ionic conductor to an electronic conductor, takes place at the counter electrode (CE). The potential of the working electrode is measured with respect to a third electrode with constant potential: the reference electrode (RE). The potential drop between the working electrode and the reference electrode is composed of the potential drop across the double layer (ϕ_{DL} , subsequently called electrode potential or double-layer potential) and the Ohmic drop in the electrolyte (Figure 1b). For the potentiostatic operational mode, the voltage U between the working electrode and the reference electrode is controlled by a potentiostat, and the current is measured. For galvanostatic experiments, the total current flowing through the cell is kept constant and the voltage is measured between the working electrode and the reference electrode.

If the Ohmic drop in the electrolyte between the working electrode and the reference electrode cannot be neglected, the current–electrode potential (I/ϕ_{DL}) relationship, which is the curve of interest, differs significantly, sometimes qualitatively, from the measured current–voltage ($I-U$) relationship. In the 1960s it was already evident that an N-shaped dependence of the reaction current on the double-layer potential (Figure 2a) can lead to bistable behavior in the

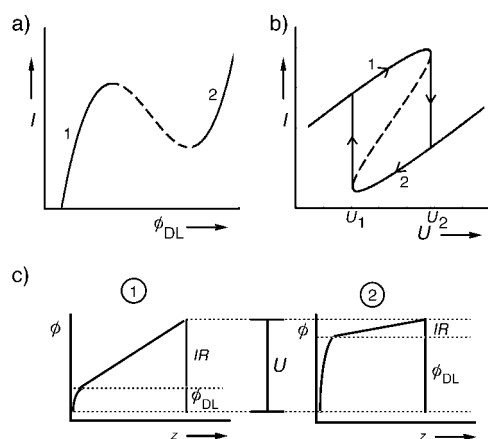


Figure 2. a) N-shaped current versus electrode potential relationship. The NDR range is depicted as a dashed line. b) Bistable current-voltage curve. c) Distribution of the applied voltage in terms of the electrode potential and the potential drop in the electrolyte for the two coexisting stable states.

current-voltage relationship if the cell resistance exceeds a threshold value (Figure 2b): Three combinations of double-layer potential and Ohmic voltage drop exist in a certain range of the external voltages. For these combinations, the potentiostatic control condition $U = \phi_{DL} + IR$, is met. The state corresponding to the medium current value is then on the negative differential resistance of the i/ϕ_{DL} curve and is unstable, which means it cannot be realized experimentally. The two stable stationary states are at branches 1 and 2 of the i/ϕ_{DL} curve, where it has a positive slope (Figure 2c).

The instability is the result of the interaction between the negative differential resistance (NDR) of the i/ϕ_{DL} relationship and the potentiostatic mode of operation. Imagine the system takes a state on the NDR branch (dashed line in Figure 2a). In this case, a small perturbation of ϕ_{DL} to somewhat higher values then results in a decrease in the stationary current and, therefore, in a decreased IR drop in the electrolyte. If the decrease in the IR drop is larger than the increase in the double-layer potential arising from the fluctuation then $\phi_{DL} + IR < U$. The working electrode is thus instantly charged (because of a feedback of the potentiostat) and ϕ_{DL} is pushed to even more positive values. However, at the more positive value of ϕ_{DL} the reaction current is even smaller, such that the described process is enhanced until a state is reached on the outer branch with positive slope (2). The control condition is met in this state, and it is stable with respect to small fluctuations.

Analogous to this, the system reaches a state on the external branch with low potentials (1) if ϕ_{DL} decreases as a consequence of the initial fluctuation. Thus, a small perturbation of the stationary state on the NDR branch is enhanced. As with autocatalytic reactions, the temporal change of the double-layer potential is proportional to its actual value upon linear approximation, whereby the proportionality constant is positive. Thus, ϕ_{DL} is an autocatalytic variable here.

Bistability in a homogeneous system is essentially always connected to autocatalysis, and is independent of the type of system. Therefore, all chemical systems that display bistability have a reaction step in which an intermediate enhances its own production.^[16] Thus temperature can take on the function

of the self-enhancing variable in exothermic, homogeneously or heterogeneously catalyzed reactions.^[17] The temporal evolution of the potential drop at an interface in many semiconductors^[18] or membranes^[19] is responsible for the positive feedback, a process that is analogous to the electrochemical systems described above.

Dynamic instabilities are often found in electrochemical systems because of the ease with which a negative differential resistance forms.^[11] It occurs, for example, if the surface of the electrode becomes chemically altered because of a change in the electrode potential in the direction of higher overpotential such that the rate of the electrochemical reaction is reduced. This is the case for the best known electrochemical oscillators, the metal dissolution reactions, where the oxidation rate of the metal is reduced or even fully inhibited because an oxide layer forms. Other causes for the formation of a negative differential resistance can be adsorption of a nonreactive species dissolved in the electrolyte, such as an ion of the conducting salt. In addition, electrostatic interactions with charged reactants or the potential-dependent desorption of a catalyst can result in a negative differential resistance.

Three experimental examples of bistable i/U plots are depicted in Figure 3. Figure 3a shows a cyclic voltammogram of the reduction of peroxodisulfate at an Ag electrode. For this system, the negative differential resistance responsible for

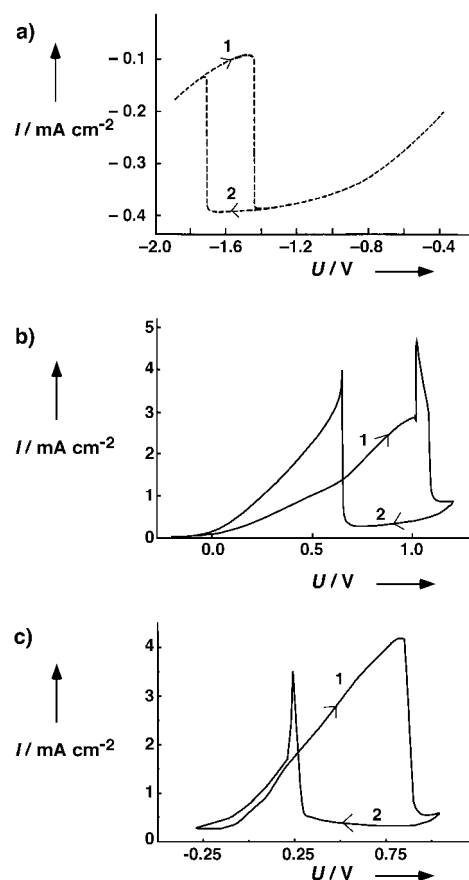


Figure 3. Experimental examples of bistable current-voltage curves: a) reduction of $S_2O_8^{2-}$ on Ag; b) oxidation of H_2 in the presence of Cu^{2+} and Cl^- ions on Pt; c) formic acid oxidation on Pt. U is given versus the SCE. (Figure 2c was generously provided by P. Strasser; see also ref. [77]).

the bistability arises from the electrostatic repulsion of the peroxodisulfate ions at potentials at which the electrode is negatively charged.^[20] Figure 3b shows the current–voltage curve of hydrogen oxidation on a Pt electrode in the presence of Cu^{2+} and Cl^- ions. Here, the adsorption of chloride ions results in a decrease in the oxidation current of the active branch 1 at about 1.2 V. As a consequence, the double-layer potential increases and reaches a range where formation of PtOH takes place. This results in an inactive electrode (branch 2). (The current peak just before the transition to the inactive branch is caused by the interaction between Cu and chloride ions on adsorption.^[21])

Negative differential resistance and, thus, bistability during the oxidation of formic acid (Figure 3c) are also caused by the formation of a nonreactive PtOH electrode. Besides the electrooxidation of iron, cobalt, or nickel, the three systems listed above are the ones whose spatiotemporal behavior has been most investigated. Therefore, we will run into these systems time and again in this review.

2.2. Accelerated Fronts by Nonlocal Migration Coupling

A local perturbation or a fluctuation in a homogeneous stationary state triggers a front if the perturbation has a critical size and passes a threshold value.^[14, 15] The motion of the front, as well as the occurrence of all other patterns discussed here, arise because of the interaction of the homogeneous system dynamic and lateral transport processes. For a bistable case, this can be visualized with a simple schematic (Figure 4): Imagine a bistable system being partly

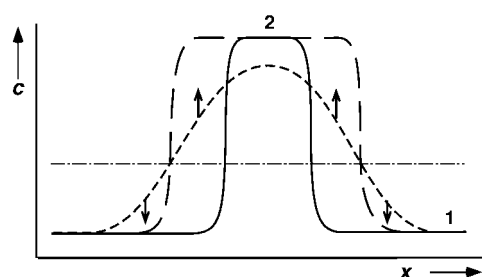


Figure 4. Development of a front in bistable media by interaction of an autocatalytic reaction and a transport process.

in one of the two stable states and partly in the other state (solid line). A gradient in the autocatalytic variable then exists in the transition region of the two states. If we assume that this is a concentration then the concentration gradient leads to a particle flux, which would result in an adjustment of the concentration difference without the autocatalytic reaction step. Thus, diffusion causes a lateral expansion of the transition range (line with short dashes). However, the autocatalytic kinetic acts against this homogenizing process: Autocatalysis causes all ranges in which the concentration is above a certain threshold (the unstable stationary state, dotted line with dashes) to evolve toward stationary state 2. All ranges below this threshold evolve toward state 1 (arrows). These processes, which actually take place simulta-

neously, result in the propagation of the transition range, that is, in a front: The more stable of the two states (state 2 in Figure 4) expands while the region of the metastable state decreases (line with long dashes). Moreover, the front profile and the propagation velocity remain constant. Both are determined by the parameters of the system, which normally are rate constants and diffusion constants.^[14, 15]

In electrochemical systems with N-shaped current versus double-layer potential curves, the double-layer potential ϕ_{DL} is the central and autocatalytic variable. Accordingly, the fronts are potential fronts. An inhomogeneous potential distribution of ϕ_{DL} affects the distribution of the potential in the whole electrolyte. The potential distribution in the electrolyte is determined by the electroneutrality of the electrolyte. Therefore, a change in the distribution of the double layer potential also changes the migration currents at the electrode/electrolyte interface.^[22] These changes cause a position-dependent recharging of the double layer. They are thus responsible for the occurrence of fronts in bistable systems. Hence, the patterns arise as a result of the interaction of the migration and the dynamic of the homogeneous system described in Section 2.1. The manifestation of the reaction–migration fronts, however, normally differs from the typical reaction–diffusion fronts. The variation in the reaction–migration fronts is bigger than that of reaction–diffusion fronts. This can be seen when experimental examples are compared (Figure 5).

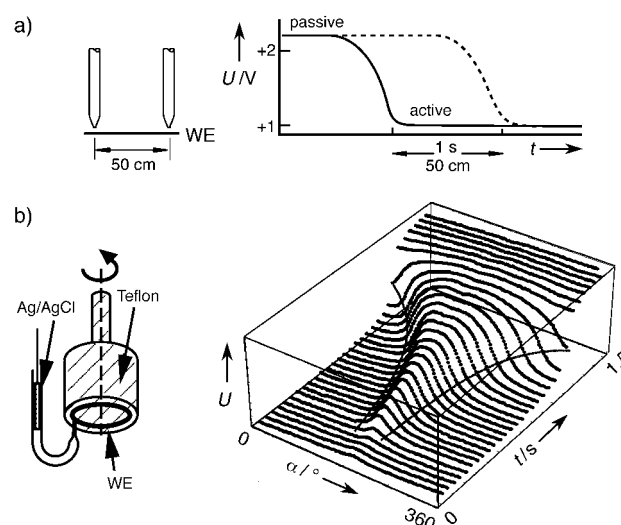


Figure 5. Experimental potential fronts a) during the corrosion of gold in a concentrated HCl/NaCl solution (according to ref. [23]), b) during the potentiostatic reduction of $\text{S}_2\text{O}_8^{2-}$ on an Ag ring electrode in dilute electrolyte.^[22] On the left are the corresponding experimental setups.

Figure 5a shows plots of potential versus time for the electrodisolution of gold at two positions of a wire 50 cm apart.^[23] The large drop in the electrode potential by more than 1 V is the result of a passing passive front. This front passes the second potential probe one second later. Both curves are of an identical shape, which implies there is a constant front profile as well as a constant velocity.

In contrast, an increase in the velocity with which the potential fronts propagate across the electrode can be seen clearly in the temporal evolution of potential profiles (Fig-

ure 5b, right). These potential profiles were recorded in front of a ring electrode during the reduction of peroxodisulfate.^[22] The spatial resolution was obtained with a single measuring probe over which the ring electrode was rotated (Figure 5b, left). The rotation of the ring electrode further ensures a defined mass transport. Accelerated fronts of the potential have since been found for several systems such as for cobalt^[24] and iron dissolution.^[25, 26]

The different propagation behavior of electrochemical fronts compared to fronts in reaction–diffusion systems is a consequence of a different range of spatial coupling.^[12, 27] As mentioned above, the coupling of the electrode to the electrolyte plays the most important role for the spatial coupling in electrochemical systems: An inhomogeneous distribution of double-layer potential also induces a potential pattern in the electrolyte. This potential pattern adjusts itself such that the electrolyte (outside of the double layer) always stays electroneutral. The potential pattern reaches up to the counter electrode, and hence we can assume that an equipotential plane exists in front of the counter electrode. The amplitude of the potential pattern in the electrolyte decreases with increasing distance from the electrode and expands parallel to the electrode at the same time (Figure 6a,

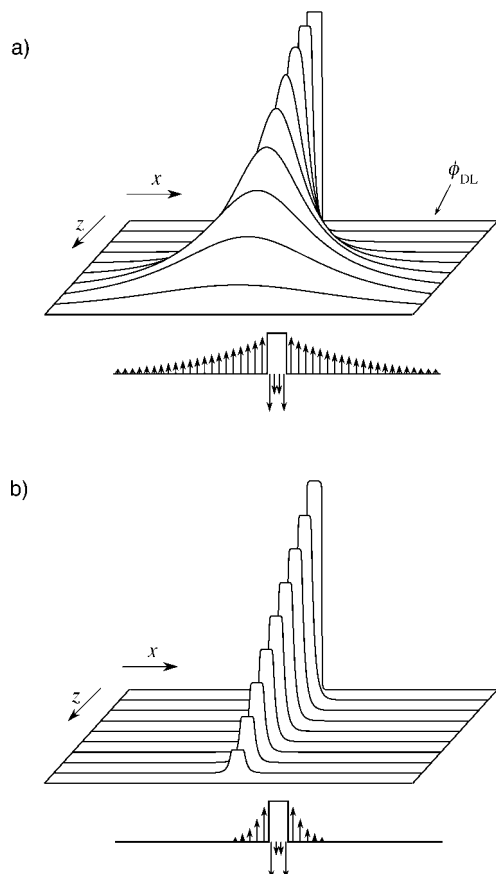


Figure 6. Schematic representation of the potential distribution in the electrolyte as a result of an inhomogeneous distribution of the electrode potential ϕ_{DL} , and the effect of migration currents induced by the inhomogeneous potential distribution on the local temporal evolution of the potential a) for the case that the ratio of the distance WE/CE to the length of WE is > 1 , b) for the case that this ratio is $\ll 1$. (x , z : spatial coordinates parallel and perpendicular to the electrode, respectively. The electrode is assumed to be one-dimensional and the electrolyte two-dimensional.)

top). The expansion is also felt at the electrode/electrolyte interface in the form of changed migration current densities. Intuitively it becomes clear that the migration coupling encompasses a wide range of the electrode, sometimes even all of the interface. This situation is illustrated in the bottom portion of Figure 6a. The length of the arrows indicates schematically the instantaneous contribution of migration coupling to the recharging of the double layer. Spatial coupling in electrochemical systems is therefore long-range or nonlocal: A perturbation of the state of the electrode at a certain location x_0 instantaneously causes a change of states at locations far away from the disturbance. The closer a given location is to x_0 , the larger the change at this location.

The range of the migration coupling depends on the ratio of the size of the working electrode (the length of the electrode for an essentially one-dimensional electrode or the circumference for a ring electrode) to that of the distance between the working electrode and the equipotential plane, normally the counter electrode. The closer the counter electrode and working electrode are, the less noticeable is the expansion of the potential pattern parallel to the working electrode (Figure 6b, top). This leads to a smaller range of the spatial coupling (Figure 6b, bottom). In the limit of vanishing distances between working electrode and counter electrode, the nonlocal coupling changes to a nearest-neighbor coupling or local coupling, in which only an infinitely small environment immediately feels a noticeable contribution of the spatial coupling.^[12, 27] This is also the situation seen with diffusive coupling. In this sense, diffusion coupling is a local coupling.^[14]

The nonlocal coupling is the reason why electrochemical fronts usually do not propagate with constant but with increasing velocity.^[27] The motion of the front is therefore accelerated if the distance between the working electrode and counter electrode is large. This situation applies to most experimental setups and was also the case for the measurements presented in Figure 5b. At the time the measurements shown in Figure 5a were carried out the connection between cell geometry and propagation behavior of fronts was not yet known, and the relative location of the electrodes can unfortunately no longer be reconstructed. However, since a wire of more than 50 cm in length was used as a working electrode in the experiment, it is likely that the ratio of the distance between the working and counter electrode (or the equipotential plane parallel to the working electrode) relative to the length of the electrode was $\ll 1$. Thus, conditions probably existed in which the migration coupling can be approached by a diffusion coupling.

2.3. Control of Front Speed by Global Coupling

Aside from local or nonlocal coupling, global coupling also often exists in chemical and physical systems, especially if one variable is subject to external control. Global coupling means that the change of the state at a particular location is instantly and equally affected by a certain change of the state at any arbitrary location. In the last few years it has been demonstrated by theoretical investigations as well as by experiments

that global coupling in different dynamic situations can have an enormous effect on the spatiotemporal dynamic of a system, such as for heterogeneously catalyzed reactions, for semiconductors that were particularly similar to electrochemical systems^[28, 29], or for gas discharge systems.^[30]

Individual locations of the electrode can be coupled globally in electrochemical experiments by the potentiostatic as well as the galvanostatic mode of operation.^[31–34] The explanation for this may be obvious for galvanostatic systems: If the current density changes at a particular location, the total current changes. As soon as the latter differs from the set current, the galvanostat varies the potential of the electrode. This variation immediately leads to a change in the potential drop across the double layer at all locations of the electrode, and, thus, to a global coupling of the individual locations of the electrode. For the potentiostatic mode of operation, the global coupling becomes important if the reference electrode is close to the working electrode. This can be understood better if one recalls that a local change of the double-layer potential changes the potential distribution in all of the electrolyte. This change is bigger at the working electrode than farther away from it. Consequently, if the reference electrode is close to the working electrode, a local change of the double-layer potential causes the set voltage between the reference and the working electrode to differ from the actual voltage. Therefore, the change causes the potentiostat to vary the potential of the working electrode. This scenario is analogous to the galvanostatic case, and the result is a change of the double-layer potential along all of the electrode.

Here we should mention that we implicitly assumed that the reference electrode is far away from the working electrode in the examples in Section 2.2. Thus, the above-mentioned global coupling does not influence the dynamic in the examples. The front behavior changes qualitatively if global coupling is present, as we will discuss below.

For global coupling, the temporal evolution of a local state depends generally on the spatial mean of a variable. In the case of electrochemical systems, the partial differential equation for the dynamic of the double-layer potential contains a term of the form $\alpha\langle\phi_{\text{DL}}\rangle$, where the brackets symbolize that the average is formed. α is a parameter that is dependent on various system parameters such as the specific conductivity of the electrolyte and displays the strength of the global coupling (see Appendix). It can be seen from the corresponding equivalent circuits that the sign of α is positive under galvanostatic control^[34] and negative under potentiostatic control for a close reference electrode.^[31] Thus, one speaks of positive and negative global coupling.

The sign of the global coupling influences the effect of the coupling. Again, this can best be shown for a transition in the bistable regime. The starting point for our considerations is the situation depicted in Figure 4, that is, a bistable system in which a small range underwent a transition from the original homogeneous state 1 to state 2. If state 2 has the larger value of the double-layer potential, the nucleation of state 2 results in a larger mean value $\langle\phi_{\text{DL}}\rangle$. As a consequence, all locations originally in state 1 experience a change in the direction of larger values of ϕ_{DL} for positive global coupling. This leads state 1 to drift to larger values. However, above all, the

transition from state 1 to state 2 is accelerated close to the front since a broader range is lifted above the threshold value as a result of the concerted action of migration coupling and global coupling. The self-accelerating effect of the transition can be seen: In the next time step the mean value increases further as does the speed with which the locations close to the front skip to state 2. In extreme cases, namely, for very big values of α , this leads to an essentially homogeneous transition whereby practically the whole electrode is driven to state 2 after its nucleation. Overall then, we note that the front acceleration is enhanced for positive global coupling.

For negative global coupling everything is reversed: When state 2 nucleates, positions in state 1 are driven to smaller values of ϕ_{DL} , that is, farther away from state 2. Accordingly, the effect of the migration coupling, which is still present, is reduced in the transition region of states 1 and 2. Without global coupling its interaction with the homogeneous dynamic would result in the propagation of state 2. Thus, the propagation speed of the front is reduced in the presence of a negative global coupling. Beyond a threshold of the coupling strength $|\alpha|$, the velocity of the front can become zero. In that case a stationary dissipative structure arises: Two ranges with different ϕ_{DL} coexist on the electrode. Figure 7 shows two experimental examples of stationary domains of the potential that formed spontaneously when a close reference electrode was used. At the bottom of the figure the corresponding current–voltage plots are presented. The arrow indicates the value of the voltage for which the spatiotemporal data were obtained.

The data of Figure 7a were measured during the reduction of $\text{S}_2\text{O}_8^{2-}$ at an Ag ring electrode with the same experimental setup as the accelerated fronts of the potential depicted in Figure 5b (except for a closer reference electrode).^[31] The effect of the position of the reference electrode on the front behavior is particularly impressive when these two figures are compared. Figure 7b shows data obtained during the oxidation of H_2 at a Pt electrode in the presence of Cu^{2+} and Cl^- ions. A rotating ring electrode was used in this experiment as well, and the spatiotemporal data were measured with a setup analogous to that shown in Figure 5b. In addition, one can see in Figure 7b how the corresponding domains evolve from a homogeneous state after the external voltage has been set. The formation of the potential domains was observed for both systems in the voltage range in which the transition between the branches with high and low current density takes place. The ratio of the size of the two domains changes continuously if U is varied in this range.^[31, 35]

The experiment depicted in Figure 8a shows very clearly the effective influence of synchronizing migration coupling and negative global coupling. The data were obtained during the oxidation of formic acid at a stationary Pt ring electrode in the bistable regime of the reaction using a close reference electrode.^[36] The local potential was measured in this experiment with the help of 11 stationary potential probes. These probes were placed, together with a trigger electrode at position 12, over the ring electrode (Figure 8b). The double-layer potential was pushed further into the passive range at the locations marked by arrows (the ring position $12 \triangleq 0$) by a pulse produced with the trigger electrode at time 0. This caused a transition to the active state at the 180° position, that

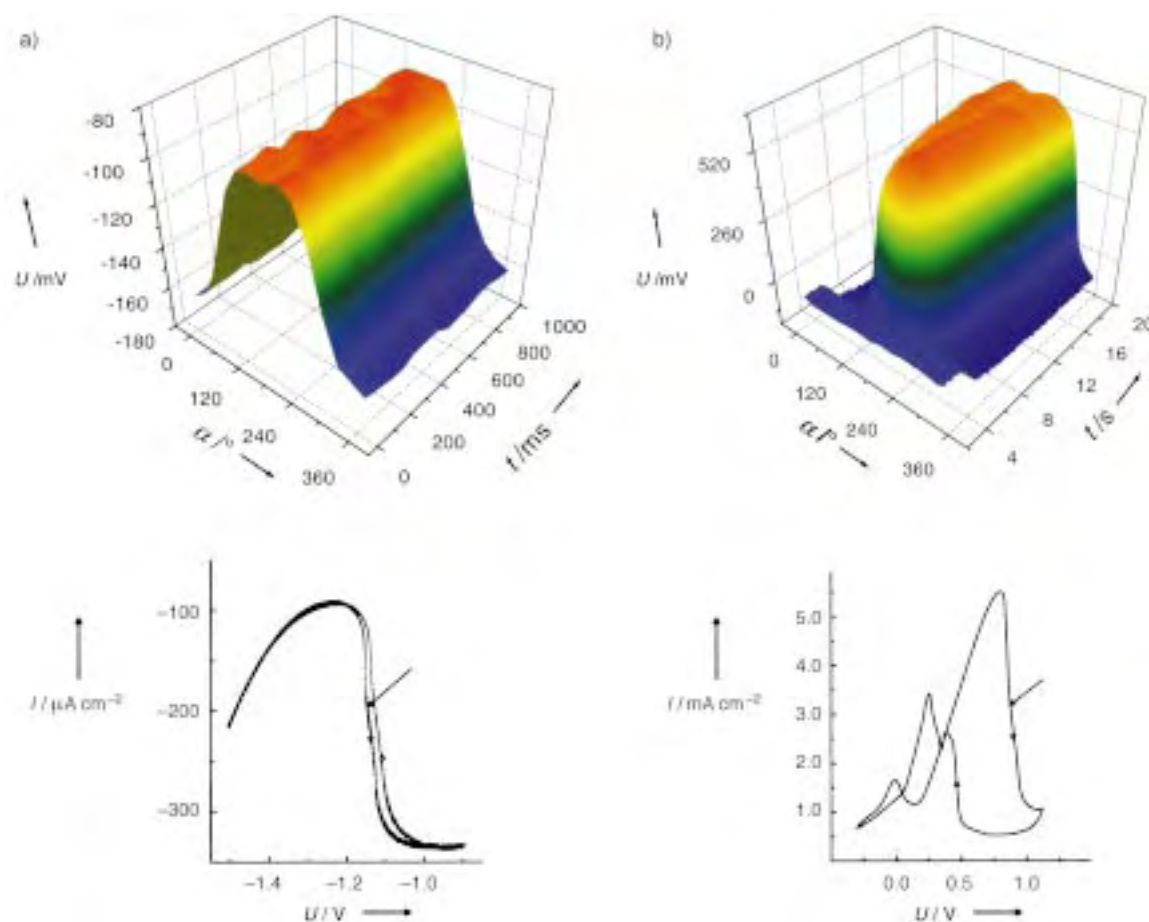


Figure 7. Stationary potential domains measured with a Haber–Luggin capillary (that is, a centric RE close to the WE) a) for the potentiostatic reduction of $\text{S}_2\text{O}_8^{2-}$ on an Ag ring electrode,^[31] b) for the potentiostatic oxidation of H_2 on Pt in the presence of Cu^{2+} and Cl^- ions. At the bottom are the corresponding cyclic voltammograms obtained for this electrode arrangement. The arrows indicate the values of the voltage for which spatiotemporal data were obtained (in stationary measurements). See Figure 5b for the experimental setup.

is, exactly opposite the disturbance. This phenomenon, known as remote triggering, shows that the further away the positions are from the reference position the more pronounced is the antiphase behavior induced by the negative coupling, since at these positions the migration coupling, which opposes the negative coupling, is the smallest.

As we have seen, fronts in electrochemical systems show many different types of behavior depending on the experimental conditions and the arrangement of the electrodes. These behavior types are summarized in the simulations depicted in Figure 9. Standing domains form because of a close reference electrode and, thus, because of strong, negative global coupling as calculated by Christoph^[35] (a). If the global coupling becomes weaker as the result of an increased distance of the reference electrode the transitions in the bistable regions are accompanied by fronts. The speed of these fronts decreases during the transition (b). For a remote reference electrode but close counter electrode (or equipotential plane), the migration coupling is local and, thus, the fronts move at a constant speed (c). If the distance between the working electrode and counter electrode is successively enlarged, the fronts are increasingly accelerated (d). Under galvanostatic conditions, namely, in the presence of a positive global coupling, the transition between both states takes place almost homogeneously (e).

3. Waves in Oscillatory Media

So far we have limited ourselves to phenomena that can be described by the spatiotemporal evolution of a single variable. Oscillating behavior and most wave phenomena arise because at least two variables interact. Simple periodic oscillations are often the result of so-called activator–inhibitor kinetics, especially in chemical reactions and in the electrochemical reactions presented here (Figure 10).^[14] An activator is a variable that catalyzes its own production (thus it is autocatalytic), and that at the same time activates the formation of the inhibitor, that is, the formation of a second species (or variable). In contrast, the inhibitor impedes—or inhibits—the growth of the activator, and decays at a certain rate. The interaction between the activator and inhibitor represents a negative feedback mechanism: the activator induces its own decomposition through the formation of the inhibitor. Overall then, oscillatory behavior usually occurs together with autocatalysis and a negative feedback mechanism. The interaction of activator–inhibitor kinetic and transport processes or global coupling eventually results in chemical or electrochemical waves.

Electrochemical nonlinear phenomena can largely be placed into two classes of models:^[37] The first class encom-

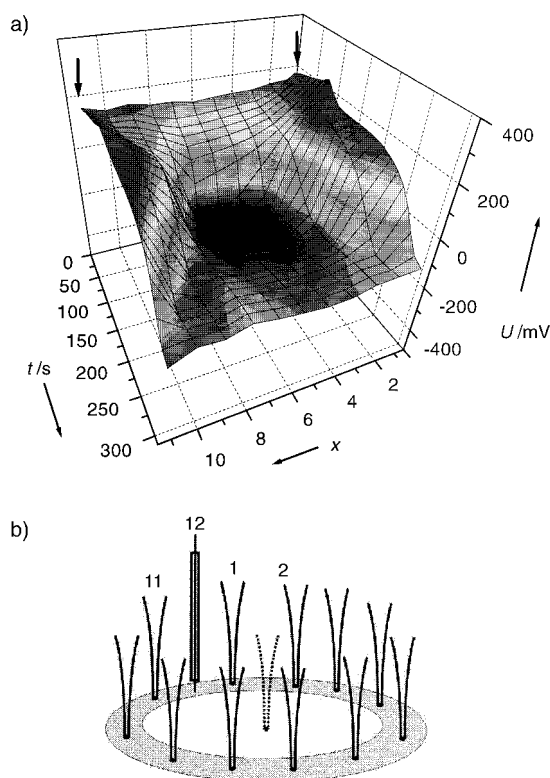


Figure 8. a) Local potential as a function of position and time during a remotely induced transition in the bistable regime of the oxidation of formic acid on a Pt ring electrode. The RE was positioned close to the WE. At the positions marked by the arrows the potential was disturbed locally toward positive values. The ring position gives the electrode number of (b). b) Setup for measurements used to obtain the data of (a). The outside potential probes serve to measure the local potential, the central one serves as the reference electrode. (This figure was provided by courtesy of P. Strasser and M. Eiswirth; see also ref. [36].)

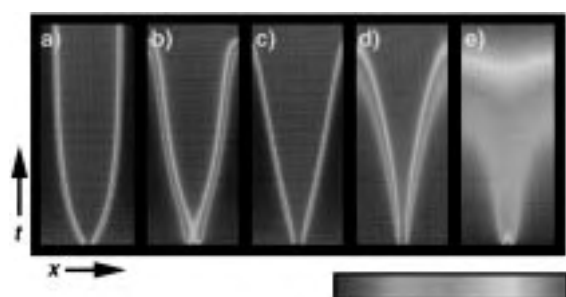


Figure 9. Simulation showing the influence of coupling on front behavior: a) for overcritical, negative global coupling, b) for less than critical, negative global coupling, c) without global coupling and a small distance between WE and CE (that is, approximate local migration coupling), d) without global coupling and a large distance between WE and CE (nonlocal migration coupling), e) under galvanostatic conditions, namely, with positive global coupling. The bar indicates the non-monotonic gray scale used.

passes systems that are connected to an N-shaped I/ϕ_{DL} curve and are known as N-NDR systems. As discussed above, such a relationship is linked to a self-enhancing change of ϕ_{DL} in certain ranges of the potential; ϕ_{DL} takes the role of the activator for N-NDR systems if two or more variables are necessary to describe the dynamic. Temporal and spatiotemporal dynamics of this type of oscillation are presented in this

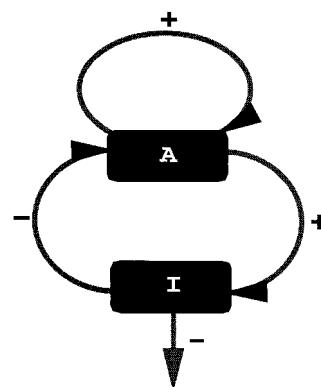


Figure 10. Positive (+) and negative (–) feedback between the activator (A) and inhibitor (I) variable.

section. The second class is connected to an S-shaped I/ϕ_{DL} curve, and ϕ_{DL} can be identified with the inhibitor.^[38] The inhibitor is especially important for the formation of Turing-like stationary structures, and will be introduced in Section 4.1.

3.1. Homogeneous Dynamic

We can already find oscillations in N-NDR systems if the reaction current is determined to a large extent by the mass transport of the reacting species. The concentration of the reacting species takes the role of the inhibitor in N-NDR oscillations.^[11] Figure 11 shows how the feedback of a slow

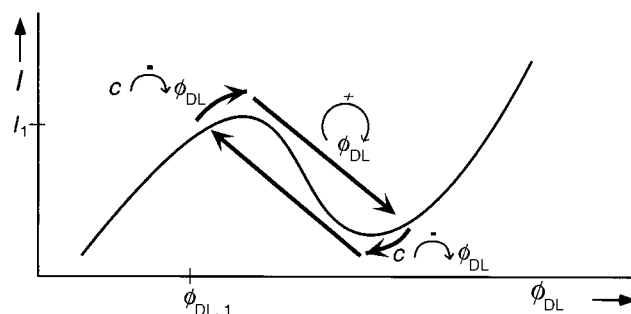


Figure 11. Illustration of how oscillations occur in N-NDR systems as a result of the interaction of electrode potential and concentration in the case of the slow transport of the reacting species.

mass transport onto ϕ_{DL} can lead to oscillations. The depicted N-shaped I/ϕ_{DL} curve represents a “base” relationship, in which base means that the concentration of the electroactive species has the same value in the reaction plane for all potentials. This situation corresponds to the limiting case of infinitely fast transport. For slower transport, however, the concentration of the reactant in front of the electrode will be reduced the most at potentials for which the current is the largest. Let us assume that at the start of an experiment, that is, at a time when the concentration in front of the electrode equals that of the bulk, a state would be taken on the first branch of the I/ϕ_{DL} curve relatively close to the current maximum (for example, $I_1/\phi_{DL,1}$ in Figure 11). The consump-

tion of the reactant would initially be larger than the replenishment by the transport; the concentration and, thus, the current would therefore decrease slowly. However, the potential drop in the electrolyte is smaller for a lower current density, which results in an increase of ϕ_{DL} under potentiostatic conditions. Therefore, ϕ_{DL} is pushed to higher values because of the slow transport. If ϕ_{DL} reaches the range of negative differential resistance ϕ_{DL} is “produced” autocatalytically according to the same mechanism discussed in Section 2.1 for bistable behavior. This “production” continues until ϕ_{DL} takes values on the outer branch of the N curve. The current is much less for these values than for our starting potential, and the concentration of the electroactive species increases again at this low reaction rate. Accordingly, the current then increases slowly, and thus, the potential moves to lower values until autocatalysis starts up again. In this way, the system reaches a situation similar to that of the starting situation, and the cycle starts anew.

Oscillations in all oscillating systems occur only in certain ranges of the external parameters. For example, the conductivity of N-NDR systems cannot be too large or too small. It should be mentioned, however, that the only demand on the electrode kinetic is still the occurrence of a negative differential resistance. This is part of the reason why oscillations appear much more often in electrochemistry than, for example, in chemical reactions in a homogeneous phase. However, potential-dependent processes that take place at the interface often also result in a negative feedback.^[7, 8, 39, 40] These latter electrochemical systems have a different phase or bifurcation diagram in the parameter plane spanned by the external voltage and the electrolyte resistance than the systems discussed above.^[7, 8] The biggest difference is that these systems oscillate under galvanostatic conditions, which is in contrast to the oscillator-type we looked at above. A current–voltage relationship with a negative impedance is also a necessary prerequisite for this type of oscillator. However, in the stationary current–voltage curve, this negative impedance is visible only in a subsystem. Other electrode processes take place in the total system in parallel to the reaction steps of the subsystem and cover the typical N-shape or at least a region of the negative differential resistance. If the steps hiding the negative differential resistance are slow compared to typical changes of ϕ_{DL} , the stationary I/U relationship becomes unstable under galvanostatic conditions and for high values of electrolyte resistance (or, generally, for a sufficiently large resistance in series to the working electrode). Furthermore, oscillations occur. Since the negative differential resistance does not surface in the range of the oscillations for the total system, the connotation for this N-NDR subsystem has an additional “H” (for hidden) to differentiate it from the systems described above.^[8, 39]

Typical representatives of HN-NDR oscillators are oxidation reactions of small organic molecules such as formic acid,^[41, 42] formaldehyde,^[43] or methanol.^[44] Furthermore, the electrochemical dissolution of nickel^[7, 45, 46] or the oxidation of hydrogen in the presence of certain cations and anions^[8] can be attributed to this oscillator type.

As we have seen, bistable behavior in N-NDR systems turns into oscillatory behavior only because the rate of the

electrode reaction becomes transport-limiting. In the case of an HN-NDR oscillator, a rate-limiting transport represents a negative feedback as well. Therefore, HN-NDR systems with a mass transport limiting reaction rate often require the consideration of a third variable, the concentration of the reacting species in front of the electrode. Hence, such HN-NDR systems possess two feedback loops. Dynamic systems such as these, that is, systems with three variables: autocatalysis and two negative feedback loops, can also exhibit more complex temporal behavior.^[16]

The best known and most spectacular of these behaviors is certainly deterministic chaos. There are numerous electrochemical examples of deterministic chaotic oscillations in the potential or the current. Aside from chaotic behavior, many studies involved mixed-mode oscillations (MMOs). These are characterized by an alternating sequence of a certain number of oscillations with small and large amplitudes. A characteristic pattern of small and large amplitudes usually exists only in a small parameter interval. If an experimentally controllable quantity is changed complicated sequences are observed (Figure 12), whose underlying mathematical structure could be uncovered by a number of theoretical studies.^[47, 48]

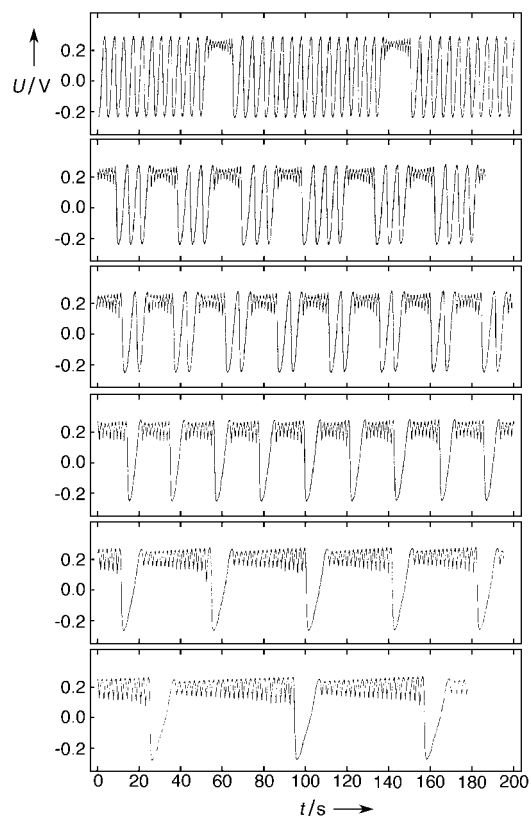


Figure 12. Mixed-mode oscillations during galvanostatic oxidation of H_2 on a Pt electrode in the presence of Bi^{3+} and Cl^- ions. The transition between the forms of oscillation was caused by a minor change in the set current.

The chemical and electrochemical processes leading to negative differential resistance or to negative feedback for HN-NDR oscillators can be discerned for a number of reactions. However, the physicochemical origin of the second feedback loop, and thus, the occurrence of chaos or MMOs

has been identified in only a few examples. It is easy to conclude that slower transport for HN-NDR systems can result in more complex temporal behavior. However, up to now, studies indicate that slower transport is not responsible for the occurrence of MMOs or chaotic oscillations under galvanostatic conditions.^[8, 42] Nonetheless, MMOs or chaotic oscillations occur with almost all HN-NDR oscillators.

In contrast, the origin of mixed-mode oscillations in the first described N-NDR oscillators appears solved and seems to be independent of electrode processes. Koper and Gaspard showed that slow transport can provide not just one but two degrees of freedom.^[49] This result can be explained by a concentration change in an expanded range in front of the electrode. The whole concentration profile perpendicular to the electrode does not adjust spontaneously to a concentration change at the electrode caused by a high reaction rate. Rather, the adjustment of concentration at larger distances shows a delay, which manifests itself as a new degree of freedom in the dynamic. Although most of the observed complex oscillations are a result of other feedback loops, we have to point out how small the demands on the electrochemical processes are in order to be sufficient enough to cause an enormous variety of dynamic features for electrochemical reactions.

3.2. Primary Spatial Instability of the Simple Limit Cycle

Altogether, the number of studies on spatial pattern formation for oscillating electrochemical reactions is relatively small—probably because of experimental difficulties. Some studies, however, provide evidence that electrochemical oscillations can be accompanied by waves. In 1844, Joule^[50] already pointed out that the periodic formation of a “white layer” observed during the dissolution of iron is not homogeneous. On the contrary, a film starts to propagate across the surface of the electrode during a certain phase of the current oscillation. Since this report, the “iron oscillator” has been renowned for exhibiting a variety of sometimes spectacular waves, such as a spatiotemporal period doubling.^[51, 52] These observations appear to be just the tip of the iceberg. The periodic variation in the current is accompanied by the formation of sometimes surprisingly complicated waves in other oscillating electrode reactions. Examples of these reactions are the electrodisolution of nickel or cobalt, the oxidation of formic acid or hydrogen, and the reduction of peroxodisulfate.^[53]

Analysis of the patterns as well as of the conditions under which spatial pattern formation takes place is normally complicated in electrochemical systems because different reaction conditions exist on the electrode boundaries compared to those at the center of the electrode. The different reaction conditions could be a consequence of a difference in concentrations or in “effective conductivity”. Thus, the parameters vary along the radial coordinate of a disk electrode.^[8, 35] The situation is different for ring electrodes: If the width of the ring is much smaller than its diameter, pattern formation takes place only along the angular coordinate. However, most observed patterns are also not under-

stood for such ring electrodes. Therefore, we concentrate on a few examples of pattern formation on ring electrodes. In this section we discuss phenomena that arise because of the interaction of migration coupling and the dynamic of the homogeneous system.^[54] In Section 3.2 we discuss phenomena that require the presence of a negative global coupling.

Let us first look at simulations that are based on N-NDR oscillators with two variables (see Appendix and Figure 13). These simulations show that the homogeneous oscillation can

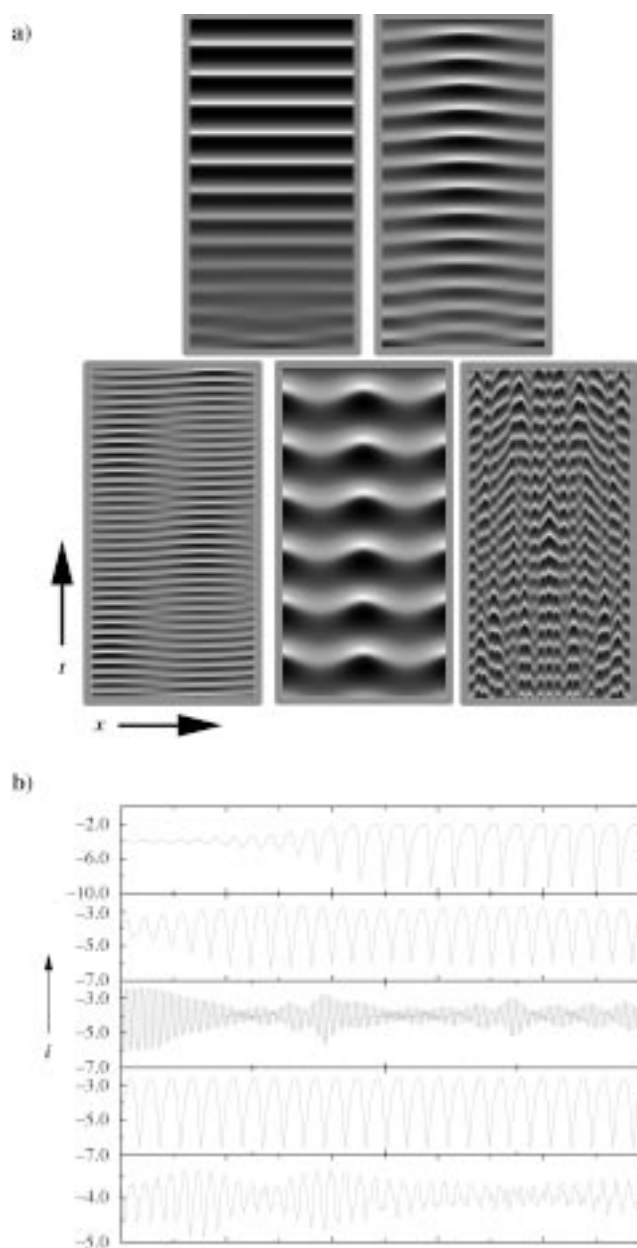


Figure 13. Simulation of a) the spatiotemporal evolution of the double-layer potential and b) the corresponding total current of an N-NDR oscillator for an electrode length that increases from left to right and top to bottom.

become unstable starting at a certain length of the electrode (Figure 13 a).^[55] The two figures in the top row document how the system becomes unstable with respect to minute spatial inhomogeneous disturbances after a minor elongation of the

electrode, which results in formation of a wave. In both cases a small sine-shaped perturbation was added to the homogeneous oscillation at a certain time. Clearly, the disturbance is dampened in the first picture, whereas a spatiotemporal structure forms in the second example. This structure can best be described as a superposition of the homogeneous oscillation and a sine-shaped standing wave. A further increase in the length of the system leads to a complicated sequence of aperiodic and periodic waves; three examples are seen in the bottom row of Figure 13a.

Figure 13b shows the total current that corresponds to the spatiotemporal plots of Figure 13a. Two things should be pointed out here: First, the primary instability of the homogeneous oscillation cannot be discerned from the global time series; in the first two situations the time series are simple-periodic after a transient time, which depends on the chosen starting conditions. Second, the time series of the total current corresponding to the aperiodic spatial evolution of the double-layer potential are not simple-periodic. Thus, the dynamic can very well get complex in the model with two variables if spatial instabilities participate. Above we stated that one needs the interaction of at least three variables for more complex behavior; this is true only for the homogeneous case. The spatial coordinate provides the system with additional degrees of freedom, which make it possible to have a not completely synchronous evolution of the individual positions.

The critical electrode length at which wave phenomena develop at the electrode depends on the parameters of the system, especially the rate constants as well as the conductivity of the electrolyte. We should stress that so far the observed wavelengths were in the range of mm to cm, that is, in macroscopic and not in mesoscopic or microscopic dimensions. Exceptions to this are two systems, the dissolution of Ag-Sb alloys^[56, 57] and the oxidation of Al in the electropolishing regime.^[58]

The transition from homogeneous oscillations to spatiotemporal chaotic behavior shown in Figure 13a is characteristic for spatially expanded (unstirred) oscillating systems. Nevertheless, to the best of our knowledge, no experiments have so far proven the primary instability of a homogeneous oscillation among chemical oscillators. Recently, we achieved the first evidence in an electrochemical system, the galvanostatic oxidation of H₂ in the presence of Cu²⁺ and Cl⁻ ions on a Pt ring electrode.^[59] As for previous experiments, the setup for this experiment was analogous to the one depicted in Figure 5b. The spatiotemporal evolution of the double-layer potential can be seen in Figure 14a. For the sake of clarity the homogeneous oscillation was subtracted in this figure so that the resulting dynamic displayed shows the spatially inhomogeneous part of the potential distribution only. It is clear from Figure 14b that the oscillations have a strong relaxationlike character. The inhomogeneous structure forms mainly at the two flanks of the oscillation. The total dynamic can be viewed as a superposition of a homogeneous oscillation and a standing wave, similar to the second simulation displayed in Figure 13a.

Another impressive example was measured by Otterstedt et al. for cobalt dissolution.^[60] This example stresses the variety of phenomena that have yet to be investigated and

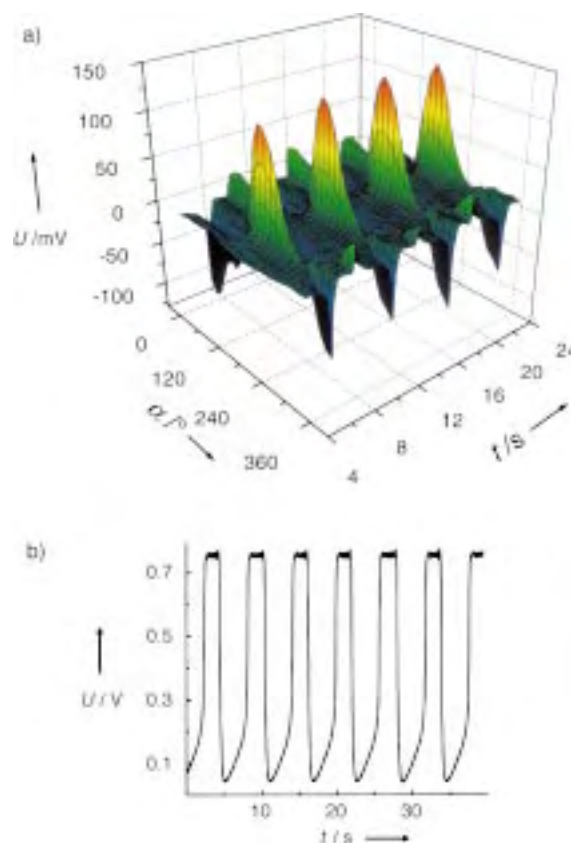


Figure 14. a) Spatiotemporal evolution of the potential at a Pt electrode during the oxidation of H₂ in the presence of Cu²⁺ and Cl⁻ ions after subtraction of the homogeneous oscillating part. b) Temporal evolution of the total current. The first four oscillations correspond to the time interval shown in (a). See Figure 5b for the experimental setup.

understood. The experiment was performed under potentiostatic conditions with a narrow cobalt strip, that is, with essentially one-dimensional electrodes. The dissolution of cobalt is oscillatory for certain values of the externally applied voltage. Current oscillations are always relaxationlike and, as long as the current oscillations are simple-periodic, active zones form at both rims of the strip. These zones expand in an accelerated fashion toward the center. This behavior appears similar to that found for accelerated transitions in the bistable regime and can probably also be explained with nonlocal migration coupling. If the parameters are varied, the activation phase becomes longer and is superposed by small oscillations (Figure 15a). These small oscillations arise from oscillations in the width of the active range: The motion of the leading front is an accelerated motion (Figure 15b); the back front displays a pulsating behavior in the passive range, however. Similar phenomena are also observed for the dissolution of cobalt in the excitable range of the reaction.^[61]

3.3. Standing Waves and Pulses through Negative Global Coupling

The spatiotemporal behavior changes qualitatively in the oscillating range if the reference electrode is close to the working electrode, that is, if a negative global coupling is

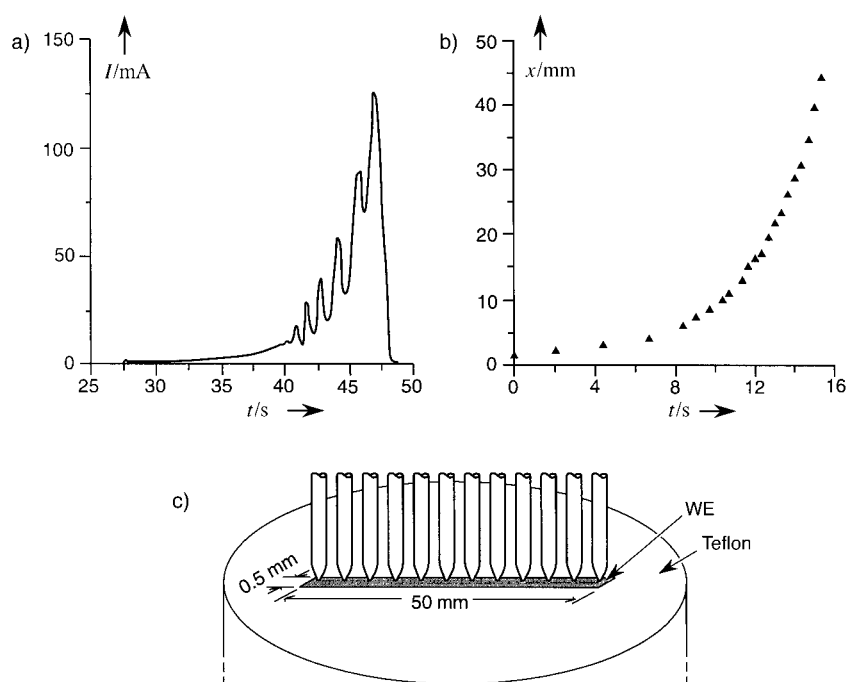


Figure 15. a) Total current and b) position of the leading front as a function of time for a single autonomous oscillation during dissolution of cobalt. c) Electrode geometry and arrangement of the potential probes to measure the spatiotemporal evolution of the potential. (Reproduced with permission from ref. [60].)

present.^[35, 62] As is immediately clear from the possibility of triggering fronts remotely (see Figure 8), regions far away from each other behave anticorrelated if a negative global coupling acts on the autocatalytic variable (in our case the double-layer potential). A homogeneous oscillation in which all positions of the electrode oscillate in phase becomes unstable at a critical strength of the negative coupling. The system then makes way for an inhomogeneously oscillating state. As a typical behavior, standing waves then occur with wave number 1 as do so-called phase pulses.

It is intuitively understood that standing waves arise because of a negative global coupling: Two domains form as a consequence of the antiphase behavior of regions remote from each other. These domains oscillate 180° out of phase. If the values of the parameters are close to those needed for the onset of oscillations, the distribution of the amplitude forms a sine structure in space. The wavelength of this sine curve is equal to the length of the system. The standing oscillation can be approximated by a sine profile oscillating in time. The sine wave possesses two nodes, that is, two positions that are stationary in time.^[63] This is a vital difference to the wave phenomena described in Section 3.2, in which the homogeneous mode is always oscillating as well. Standing waves have been observed experimentally for the oxidation of formic acid at Pt ring electrodes (Figure 16), whereby the experimental setup was analogous to that shown in Figure 8.^[64]

If besides a sine profile, the 90° -rotated structure, the cosine profile, also oscillates in time the standing wave is transformed into a phase pulse or a travelling wave. The symmetry of the system implies that the stability behavior of ring electrodes is the same with regard to sine-shaped and cosine-

shaped excitations. If both modes are excited because of an asymmetrical perturbation, a phase pulse forms.

Pulses were already measured by Otterstedt et al. in pioneering experiments with a close reference electrode.^[65] These again were experiments on the electrodisolution of cobalt. The experiments were performed with ring as well as with disc electrodes. The experimental setup was chosen such that the surface of the working electrode was facing up. Since passive and active ranges of the electrode have a visible contrast, the spatiotemporal dynamic could be followed with a video camera (Figure 17A). The pulses could be seen as narrow, travelling domains of high activity, that is, a high rate of dissolution, on an otherwise passive electrode. An example of a cobalt pulse rotating around the center of a disc electrode is depicted in Figure 17B.

Besides standing oscillations and pulses, the theoretical studies cited above predict a variety of different patterns in oscillating media with negative global coupling. Most

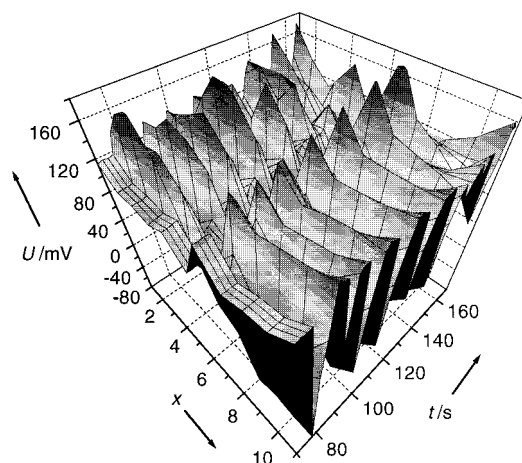


Figure 16. Standing wave for a close RE during potentiostatic oxidation of formic acid on a Pt ring electrode. See Figure 8b for the experimental setup. (This figure was generously provided by P. Strasser and M. Eiswirth, see also ref. [64].)

of them, however, exist only in substantially smaller ranges of the parameters and so far could not be proven experimentally. An exception appears to be so-called one-dimensional target patterns.^[32] For these patterns, two pulses are sent at periodic intervals from one place of the ring electrode. The pulses travel in opposite directions and cancel each other when they meet at the opposite side. A similar behavior was found likewise for the electrodisolution of cobalt, although the pulse shows aperiodic modulations in the width. The authors suspect that this is the result of the chemistry of cobalt dissolution being more complicated, and cannot be described with two variables only, unlike the assumption made for all other simulations.

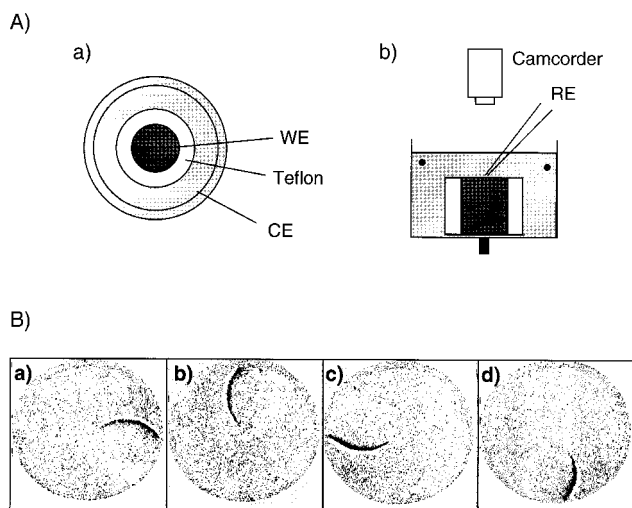


Figure 17. A) a) Top view and b) side view of experimental setup. B) Rotating active region during the oxidation of a disc-shaped Co electrode with a close RE. (This figure was generously provided by R. D. Otterstedt et al., see also ref. [60].)

4. Stationary Structures

So far we have only looked at electrode reactions that are connected to an N-shaped I/ϕ_{DL} curve, with ϕ_{DL} being the autocatalytic variable. Another type of I/ϕ_{DL} curve exists that has a negative differential resistance, but shows an opposing behavior with respect to pattern formation. These curves have the shape of an “S”, and the double-layer potential represents the feedback variable, the inhibitor. In this case, the migration coupling does not result in motion of potential fronts, but favors formation of stationary potential patterns. These patterns have a defined wavelength for sufficiently large electrodes.^[38] The wavelength is determined solely by the rate constant and by other system parameters, but not the length of the system as is the case for the stationary potential domains described in Section 2.3.

4.1. Homogeneous Dynamic

An S-shaped current–potential curve only exists if the dynamic of a chemical variable, that is, of a concentration or coverage of the electrode, is connected to an autocatalytic process that is potential-dependent. This could be a chemical, autocatalytic reaction step as was discovered for zinc dissolution, for example.^[66, 67] In addition, a self-enhancing feedback is also caused when attractive interactions between adsorbed molecules are strong enough. In this case, the adsorbing species exist in two phases depending on external parameters. The phases can be, for example, a well-ordered monolayer and a two-dimensional gas, that is, a state in which the adsorbed molecules move in an uncorrelated manner on the surface of the electrode. A transition between both phases can be induced by variations of ϕ_{DL} , for example, and takes place as a first-order phase transition.^[68] Hence, there is a certain range of potential in which both phases can coexist, one as a metastable phase and the other as a globally stable

one. These types of overcritical, attracting interactions have been found for a variety of adsorbates.^[69] If the two phases inhibit an electrode reaction differently, the corresponding current–potential relationships display an S- or Z-shaped I/ϕ_{DL} curve.

The central branch of the S-shaped curve clearly has a negative differential resistance (Figure 18a); this, together with the external potentiostatic or galvanostatic control, leads to a negative feedback loop that can stabilize a state on the

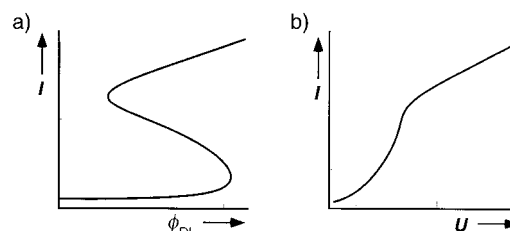


Figure 18. a) Schematic representation of an S-shaped current–electrode potential relationship. The branch with low current corresponds to high values of the potential and vice versa. b) Monotonic current–voltage curve.

NDR branch. This stabilization occurs for overcritical electrolyte resistance and manifests itself in a unique current–voltage curve (Figure 18b). The following helps to explain this: Let us assume that the system is at a state on the central potentially unstable branch of the I/ϕ_{DL} curve. Let us assume further that the system succumbs to a fluctuation toward more positive values of ϕ_{DL} . The system reacts to this perturbation foremost by autocatalytically desorbing the adsorbate (that is, we arrive at the top current branch of Figure 18a). The potentiostatic control, however, causes the increase of the current to produce smaller values of ϕ_{DL} . Thus, the fluctuation of ϕ_{DL} is suppressed.

This consideration allows us to easily see that the feedback in the potential gets so big at a critical value of the electrolyte resistance that the system periodically oscillates between the two outer branches of the I/ϕ_{DL} curve when fast changes in the coverage occur. Normally however, the characteristic time during which the potential changes is short in comparison with that of chemical concentrations or adsorbate coverage. Oscillations for systems with S-shaped current–potential curves are therefore more the exception than the rule. Rather, the system assumes a stationary state on the negative differential branch. However, this state is probably spatially structured. As will be explained in the next section in more detail, the migration coupling destabilizes the homogeneous state. For a sufficiently large electrode, these stationary, nonequilibrium patterns appear in S-NDR systems as easily as oscillations in N-NDR systems.

4.2. Turing Patterns in Electrochemical Systems

The mechanism of formation and the properties of stationary patterns of the potential are analogous to those of the famous Turing patterns.^[70] These patterns, predicted by Turing in 1952, are stationary concentration patterns that can form

spontaneously in activator–inhibitor systems if the inhibitor diffuses faster than the activator.

Figure 19 shows how the interaction of reaction and diffusion leads to formation of stationary patterns. The starting point is a homogeneous state that is slightly disturbed

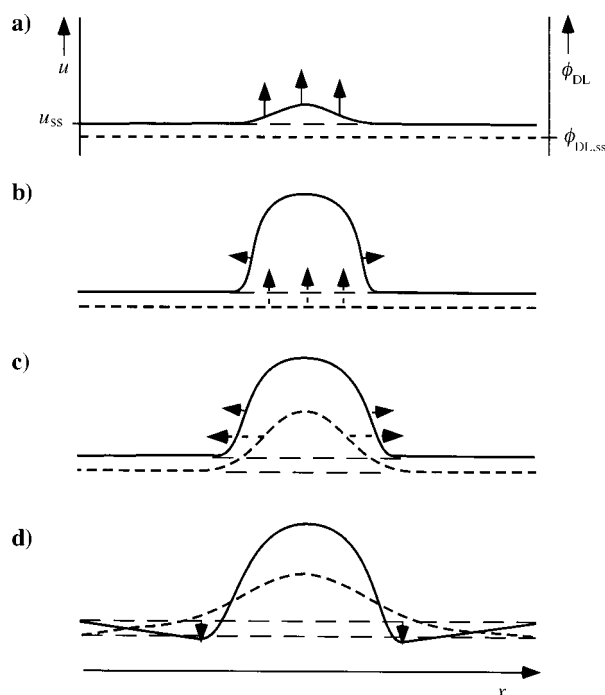


Figure 19. Evolution of a stationary structure in activator–inhibitor systems with fast transport of the inhibitor. (“ss” as well as curves with long dashes denote the value of the activator or inhibitor at the homogeneous fixed point; curve with solid line: activator profile; curve with short dashes: inhibitor profile.)

by a small local fluctuation in the concentration of the activator (solid line; a). The fluctuation is enhanced as a result of the autocatalytic nature of the activator kinetic (b). An increased activator concentration causes the inhibitor to be produced (short dashed line; c). In the S-NDR systems, for example, an increase in the coverage causes the potential to be moved to larger values, which is equivalent to the production of inhibitor. Thus, the local perturbation produces a region with higher activator and inhibitor concentration. In turn, a flux of activator and inhibitor in the neighboring region is induced. Since the inhibitor diffuses faster than the activator, the inhibitor also builds up faster than the activator in a certain neighboring region around the local spot (d). A high value of the inhibitor variable leads to a decay of the activator concentration. In our electrochemical system, for example, a high electrode potential brings about the desorption of the adsorbate.

Hence, a small local perturbation of the homogeneous state leads to a larger region of increased activator concentration because of the interaction of reaction and diffusion. Inhibitor is always produced in this region and is transported to neighboring domains. Since the inhibitor concentration is increased in the neighborhood of the local spot, the activator concentration is kept very small outside of it. In this way, a stable stationary structure arises. An outstanding property of

Turing patterns is that they are periodic patterns with a characteristic wavelength that depends solely on the reaction constants and the diffusion constants.

As we have seen, diffusion, a transport process that by itself balances any inhomogeneities over time, can destabilize a homogeneous state when interacting with certain nonlinear kinetics and can lead to the formation of concentration gradients. This fascinating fact prompted an intense search for experimental examples. However, the search for stationary Turing patterns was not successful until 40 years after Turing’s theoretical prediction.^[71] The reason for this is that it is difficult to find systems in which the diffusion coefficient of the inhibitor is sufficiently greater than that of the activator. This limitation does not exist in electrochemical systems: Here the electrode potential acts as the inhibitor, and the corresponding transport process is migration. The characteristic time of migration is always shorter than the characteristic time of diffusion^[72] of the autocatalytic species. Thus, stationary potential patterns in S-NDR systems occur almost always when the total current is in the range of the central branch of the current–potential curve (provided that the electrode is at least as big as the wavelength of the Turing structure). This has been discovered in theoretical studies only recently^[38] and were proven experimentally shortly after.^[73] A simulation of electrochemical Turing structures is shown in Figure 20. Here we stress again that these structures have a characteristic wavelength in contrast to all patterns that arise from global coupling.

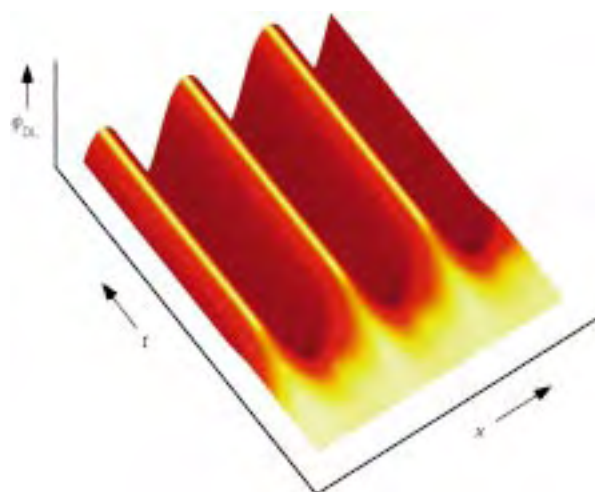


Figure 20. Simulation of spatiotemporal behavior in S-NDR systems showing the outgrowth of a stationary structure from the homogeneous state.

5. Summary and Outlook

A breakthrough was achieved in the understanding of pattern formation in electrochemical systems in the past decade. Two results caused this progress: the understanding that temporal instabilities, or, to put it more broadly, instabilities of the homogeneous system, arise in most cases because of a negative differential resistance in the I/ϕ_{DL} characteristic, and the understanding that a local change of

the potential distribution of the double layer changes the migration currents on the total electrode/electrolyte interface. Therefore, this migration coupling largely determines the formation of spatial patterns. In both cases, the electrical properties of the electrochemical systems are very important, and the electrode potential is an essential variable (that is, a variable necessary for the description of self-organization phenomena). The corresponding evolution law is obtained from the local charge balance at the electrode, and constitutes a reaction–migration equation.

Electrical properties determine the particularities of pattern formation in electrochemical systems. In contrast, the pattern formation of chemical systems in a homogeneous phase is described by reaction–diffusion systems. First let us compare the two transport processes, migration and diffusion: The conductivity of the electrolyte determines how fast inhomogeneities of the potential are adjusted by migration. The conductivity is a quantity that can be varied experimentally over several orders of magnitude. The rate of diffusion, however, is determined by the diffusion constant, whose experimental variation is very limited; it is mainly restricted to temperature changes. However, the ratio of the characteristic times of the homogeneous dynamic, that is, of the reaction term, and of the transport processes crucially influences the patterns. This influence can be investigated easily for electrochemical systems, and can be exploited to a certain degree to adjust specific patterns or to avoid spatial inhomogeneities.

The range of the coupling is a further important difference between the diffusive coupling and the coupling by migration. Diffusive coupling is a nearest-neighbor coupling; in this sense, it is local. Migration coupling, however, is nonlocal, that is, a change of state at a particular location induces noticeably and instantly changed migration currents at the electrode in an expanded, surrounding area. Nonlocal coupling thus leads to the occurrence of accelerated fronts. The extent of nonlocal coupling depends on the geometry of the cell, namely, on the distance between the working electrode and counter electrode (or an equipotential plane parallel to the electrode). The smaller this distance, the smaller the range of the coupling. In the extreme case of an infinitely small distance, nonlocal coupling turns into diffusive coupling. Thus, electrochemical systems possess the peculiarity that the range of the spatial coupling can be varied as can the characteristic time of the spatial coupling.

Two kinds of global coupling can occur aside from the migration coupling, depending on experimental conditions. If the distance between the working electrode and the reference

electrode is small the feedback over the potentiostat results in a negative global coupling. This negative global coupling induces an antiphase behavior. In contrast, a positive global coupling exists for galvanostatic conditions which acts by synchronizing itself.

All three types of coupling, migration coupling, as well as negative and positive global coupling depend solely on the electrical properties of the system. Therefore, they are independent of the electrode reaction. Thus, everything we summarized up to now applies to all electrochemical systems. The type of pattern for a given system depends on the interaction of spatial coupling and the dynamic of the homogeneous system. Here, the electrode reactions come into play. According to the present state of research, electrode reactions can be divided into just two classes under conditions for which instabilities are observed despite large chemical variations: systems with N-shaped I/ϕ_{DL} curves, and systems with S-shaped I/ϕ_{DL} curves. Both classes are activator–inhibitor systems as are chemical reactions that oscillate in homogeneous phase. The electrode potential is the activator for N-NDR systems and the inhibitor for S-NDR systems. Thus, the three types of spatial coupling discussed above act either on the activator variable or on the inhibitor variable. The variety of combinations results in a broad spectrum of spatial instabilities and patterns. These are summarized in Table 1.

If the electrode potential represents the activator, the migration coupling leads to fronts and waves, which often propagate in an accelerated manner because the coupling is nonlocal. An additional positive global coupling enhances the accelerated expansion on the one hand, and, on the other hand, can result in the formation of domains in the oscillatory range.^[74] However, if a negative coupling superposes the migration coupling then standing domains, standing waves with wave number 1, or pulses can form, depending on the parameters. If the electrode potential is the inhibitor, the migration currents can destabilize a homogeneous potential distribution in a Turing-like instability, and stationary patterns with a characteristic wavelength result. Since migration currents and positive global coupling act similarly in S-NDR systems, positive global coupling leads to the formation of stationary domains as well. The wavelength of the domains, however, is then the same as the length of the system. Negative global coupling, on the other hand, changes pattern formation only qualitatively if the system oscillates. In this case, negative global coupling can result in the formation of standing waves with wave number 1 just like in N-NDR

Table 1. Typical phenomena of pattern formation in N-NDR and S-NDR systems with different types of spatial coupling.^[a]

	Nonlocal migration coupling (always present)	Negative global coupling; potentiostatic control with Haber–Luggin capillary	Positive global coupling; galvanostatic control
N-NDR systems: ϕ_{DL} = activator	accelerated waves	stationary domains, standing waves ($n=1$), phase pulses	enhanced acceleration of potential fronts, mainly homogenizing effect; cluster formation in the oscillatory region
S-NDR systems: ϕ_{DL} = inhibitor	Turing-like structures with intrinsic wave- length ($n \geq 1$)	standing waves ($n=1$), or mixed-mode patterns with $n_1 > 1$, $n_2 = 1$; phase pulses	stationary domains ($n=1$ or $n > 1$)

[a] n is the wavenumber of the resulting pattern.

systems. For parameter values for which the migration coupling leads to the formation of Turing-like structures, the interaction of both instabilities can yield a complex wave pattern characterized by the two wave numbers $n=1$ and $n>1$.^[75] However, oscillations normally do not occur in S-NDR systems. Therefore, the latter patterns are expected to be observable only in exceptional cases.

It may appear that Table 1 contains an essentially complete summary of patterns that occur in electrochemical systems. This appearance is misleading. Table 1 only roughly summarizes results observed so far or predicted with models. These are investigations concentrating on phenomena that can be described with two essential variables (two-component systems). Furthermore, the phenomena are restricted to the basic patterns that are common and exist in a large parameter range. Additional experiments, especially in the oscillatory range, will certainly call for supplementation in the individual cells.

Moreover, the number of rows and columns of the cell will have to be increased: Numerous examples of current or potential oscillations involve complex time series. Only in a few cases does the complex time series result from the spatial patterns. Initial simulations of such behavior are depicted in Figure 13, and the first spatiotemporal structure of this series has recently been demonstrated (Figure 14). In most cases the additional degree of freedom will be from a third dependent variable such as from a concentration that adds an additional feedback loop into the system as discussed in Section 3.1. Spatial pattern formation in three-variable systems is an area that is currently developing strongly, not just in electrochemistry but generally in nonlinear dynamics. Aside from increasing the number of rows, the number of columns should also be increased. So far, it has always been assumed that concentration differences in the electrolyte can be neglected in theoretical studies as well as in the interpretation of the observed patterns. This assumption may no longer be justified for high current densities. Electrohydrodynamic convection develops from a critical current density on, and this is an additional transport mechanism that by itself leads to pattern formation and can also interact with the already discussed modes of spatial coupling.

This listing is still not complete. However, it shows some central questions and future directions in the study of self-organization phenomena in electrochemical systems. An additional, important development of research activities in the area of the nonlinear dynamic in electrochemistry is applied research. A big challenge in the next few years will be to use the knowledge obtained so far on instabilities to improve industrial processes. Here, an important and promising aspect would be to increase the yield by carrying out a reaction under conditions for which the reaction proceeds in a nonstationary or inhomogeneous manner. To apply this already old idea to electrochemical systems seems especially promising since a number of electrical parameters are available in these systems. These parameters crucially determine the dynamic and can easily be controlled experimentally. Initial experimental indications have been presented recently that suggest that nonstationary experimental conditions may actually be superior to stationary ones.^[76]

An important aspect of investigations of pattern formation in chemical systems has always been that these systems can function as models, especially for biological systems. The contribution of the investigations is, without doubt, highly significant for the understanding of biochemical oscillations, cellular rhythms, or even the formation of spatial patterns as, for example, during the developmental phase of the slime mold *Dictyostelium discoideum*. Early studies on pattern formation in electrochemical systems were motivated by the similarity of potential waves that had been observed for metal dissolution reactions and the propagation of electrical signals in the nervous system. Up to now, a central role has been assigned to the universal aspect of research of nonlinear phenomena, which establishes the continued interdisciplinary interest on chemical nonequilibrium structures. Electrochemical systems are ideal model systems for a variety of processes of pattern formation, particularly if they involve the interaction of chemical and electrical properties. Such systems are often encountered in biological systems, such as, for example, in biophysical membrane oscillations.

Appendix

In this appendix we list the minimal equations (prototype equations) that describe the phenomena of self-organization discussed in the individual chapters. Figures 9, 13, and 20 are based on these equations. All symbols used are explained at the end of the Appendix.

Section 2: The phenomena discussed in Section 2 are described by the spatiotemporal evolution of only one degree of freedom (a single variable). All examples shown here apply to N-shaped current–voltage curves, for which ϕ_{DL} is the essential variable.

The dynamic of the homogeneous system is given by Equation (1),^[7, 8] where $k(\phi_{DL})$ has an N-shaped dependence

$$C \frac{d\phi_{DL}}{dt} = -nFc_0 k(\phi_{DL}) + \frac{U - \phi_{DL}}{RA} \quad (1)$$

on ϕ_{DL} . In most cases, this dependence is described as a polynomial of third degree. The first term on the right side of the equation describes the reaction current density, the second term describes the total current normalized to a unit area. For the spatially expanded system, the last term of Equation (1) has to be substituted with the local migration current density that exists in front of the electrode [Eq. (2)],^[8] where the potential in the electrolyte is obtained by solving Laplace's Equation (3). The boundary conditions follow from the cell geometry.

$$C \frac{\partial \phi_{DL}}{\partial t} = -nFc_0 k(\phi_{DL}) - \sigma \frac{\partial \phi}{\partial z} \Big|_{z=WE} \quad (2)$$

$$\Delta \phi = 0 \quad (3)$$

For the simulations depicted in Figures 9, 13, and 20, the ring-shaped working electrode was approximated by an infinitesimally thin ring, and the electrolyte by a cylindrical surface, which was confined by the working electrode on the one side and the counter electrode on the other side

[Eqs. (4)–(6)]. ϕ_{DL} and ϕ are connected by the potentiostatic [Eq. (7)] or the galvanostatic [Eq. (8)] control conditions.

$$\phi(x + L, z, t) = \phi(x, z, t) \quad (4)$$

$$\phi(x, z = \text{CE}, t) = 0 \quad (5)$$

$$\phi(x, z = \text{WE}, t = 0) = \phi^0 \quad (6)$$

$$U = \phi_{\text{DL}} + (\phi|_{z=\text{WE}} - \phi|_{z=\text{RE}}) \quad (7)$$

$$I_{\text{tot}} = -\sigma \int_0^L \frac{\partial \phi}{\partial z} \Big|_{z=\text{WE}} dx \quad (8)$$

The potentiostatic control condition adds a negative global coupling into the system if the reference electrode is not at the level of the counter electrode. In this case, as well as in the galvanostatic case, for which the global coupling is positive^[34] Equation (2) can be rearranged such that it contains a term that is proportional to the mean of ϕ_{DL} .^[31] The proportionality factor is negative for negative global coupling and positive for positive global coupling.

Section 3: The homogeneous dynamic of the standard model for N-NDR oscillators is given by the coupled Equations (9) and (10).^[7, 8] The changes of concentration arise from

$$C \frac{d\phi_{\text{DL}}}{dt} = -nFck(\phi_{\text{DL}}) + \frac{U - \phi_{\text{DL}}}{RA} \quad (9)$$

$$\frac{dc}{dt} = -\frac{2}{\delta} ck(\phi_{\text{DL}}) + \frac{2D}{\delta^2} (c_b - c) \quad (10)$$

reaction and diffusion perpendicular to the electrode [first and second term on the right side of Eq. (10)]. In the case of the spatially expanded system, Equations (9) and (10) transform into the partial differential Equations (11) and (12),

$$C \frac{\partial \phi_{\text{DL}}}{\partial t} = -nFck(\phi_{\text{DL}}) - \sigma \frac{\partial \phi}{\partial z} \Big|_{z=\text{WE}} \quad (11)$$

$$\frac{\partial c}{\partial t} = -\frac{2}{\delta} ck(\phi_{\text{DL}}) + \frac{2D}{\delta^2} (c_b - c) \quad (12)$$

respectively.^[8] The diffusion parallel to the electrode is much slower than all other processes and is therefore often neglected. The migration currents, the last term of Equation (11), at the electrode can be determined if the potential distribution in the electrolyte is known. The potential distribution obeys Laplace's Equation (3) in good approximation. The negative global coupling discussed in Section 3.2 comes into play as a result of the control condition [Eq. (7)] if $z = \text{RE}$ and is between $z = \text{CE}$ and $z = \text{WE}$.

Section 4: Homogeneous S-NDR systems have the structure described by Equations (13) and (14), where $f(u, \phi_{\text{DL}})$ is

$$\frac{du}{dt} = f(u, \phi_{\text{DL}}) \quad (13)$$

$$C \frac{d\phi_{\text{DL}}}{dt} = -i_{\text{reac}}(u, \phi_{\text{DL}}) + \frac{U - \phi_{\text{DL}}}{RA} \quad (14)$$

bistable in ϕ_{DL} and the reaction current for a given value of u depends monotonically on ϕ_{DL} , for example, exponentially.^[38] Together with Equations (3)–(6) and (7) or (8), Equations (15) and (16) describe the dynamic of the spatially expanded system.^[38]

$$\frac{\partial u}{\partial t} = f(u, \phi_{\text{DL}}) + D_u \frac{\partial^2 u}{\partial x^2} \quad (15)$$

$$C \frac{\partial \phi_{\text{DL}}}{\partial t} = -i_{\text{reac}}(u, \phi_{\text{DL}}) - \sigma \frac{\partial \phi}{\partial z} \Big|_{z=\text{WE}} \quad (16)$$

Symbols used in the equations

A	electrode surface
C	specific double layer capacitance
c_b	bulk concentration of the reacting species
c	concentration of the reacting species in the reaction plane (at $z = \text{WE}$)
D	diffusion constant of the reacting species
D_u	diffusion constant of the autocatalytic species
i_{reac}	reaction current density
I_{tot}	total current through the cell
$k(\phi_{\text{DL}})$	rate constant multiplied by a potential-dependent dimensionless term ($k(\phi_{\text{DL}})$ shows an N-shaped dependency on ϕ_{DL})
F	Faraday's constant
L	circumference of the ring electrode
n	number of electrons transferred in the electrochemical reaction
R	cell resistance between working and reference electrode
t	time
u	autocatalytic variable (usually concentration or coverage)
U	externally applied voltage for potentiostatic control
x	spatial coordinate parallel to the working electrode
z	spatial coordinate perpendicular to the working electrode
z	(= WE/RE/CE) z position of working, reference, or counter electrode, respectively
δ	thickness of the Nernst diffusion layer
ϕ	potential in the electrolyte
ϕ_{DL}	potential drop across the double layer
ϕ^0	potential distribution at the WE at time $t = 0$
σ	specific conductivity of the electrolyte.

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In Vivo Protein–Protein Interaction Assays: Beyond Proteins**

Hening Lin and Virginia W. Cornish*

In 1989 Fields and Song introduced the “Yeast Two-Hybrid Assay”, which provides a straightforward method for detecting protein–protein interactions *in vivo*.^[1] Up until the development of the two-hybrid methodology, protein binding had been detected using traditional biochemical techniques such as co-immunoprecipitation, affinity chromatography, and photoaffinity labeling.^[2] There are three significant advantages to this *in vivo* assay which led almost immediately to its widespread use: first, it is technically straightforward and can be carried out rapidly; second, the sequence of the two interacting proteins can be read off directly from the DNA sequence of the plasmids encoding them; and third, it does not depend on the identity of the interacting proteins, and so is general.

The two-hybrid assay was based on the observations that eukaryotic transcriptional activators can be dissected into two functionally independent domains, a DNA-binding domain (DBD) and a transcription activation domain (AD), and that hybrid transcriptional activators can be generated by mixing and matching these two domains. It seems that the DNA-binding domain only needs to bring the activation domain into the proximity of the transcription start site; this suggests that the linkage between the DNA-binding and activation domains can be manipulated without disrupting activity. Thus, the linkage in the two-hybrid assay is the noncovalent bond between the two interacting proteins. As outlined in Figure 1, the yeast two-hybrid system consists of two protein chimeras and a reporter gene downstream from the binding site for the transcriptional activator. If the two proteins of interest (X and Y) interact, they effectively dimerize the DNA-binding protein chimera (DBD-X) and the transcription activation protein chimera (AD-Y). Dimerization of the DNA-binding domain and the transcription activation domain helps to recruit the transcription machinery to a promoter adjacent to the binding site for the transcriptional activator, thereby activating transcription of the reporter gene.

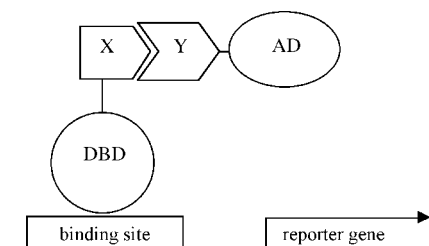


Figure 1. The yeast two-hybrid assay. DBD–X is a chimeric protein consisting of a DNA-binding domain (DBD) fused to protein X, and AD–Y is a second chimeric protein consisting of a transcription activation domain (AD) and protein Y. If protein X and Y bind to one another with reasonable affinity, the AD will be brought into the proximity of the reporter gene and will activate its transcription.

The assay was demonstrated initially using two yeast proteins known to be physically associated *in vivo*.^[1] The yeast SNF1 protein, a serine–threonine protein kinase, was fused to the GAL4 DNA-binding domain, and the SNF1 activator protein SNF4 was fused to the GAL4 activation domain. A GAL4 binding sequence was placed upstream of a β -galactosidase reporter gene. Plasmids encoding the protein fusions and the reporter gene were introduced into yeast, and β -galactosidase synthesis levels were quantified using standard biochemical assays. Control experiments established that neither the DBD and AD domains on their own nor the individual protein chimeras induced β -galactosidase synthesis above background levels. β -galactosidase synthesis levels were increased 200-fold when the DBD–SNF1 and SNF4–AD fusion proteins were introduced together. By comparison, the direct DBD–AD fusion protein activated β -galactosidase synthesis levels 4000-fold.

Since the initial paper by Fields and Song, there have been significant technical improvements in the method, and it is now an integral tool in biochemistry and genetics laboratories. For example, as a first step towards testing their hypothesis that the cyclin-dependent kinase Cdc20 is the target for the spindle checkpoint in budding yeast, Murray and co-workers used the yeast two-hybrid assay to determine if any of the proteins known to be involved in the spindle checkpoint physically interact with Cdc20.^[3] By facilitating the discovery of cascades of interacting proteins—in this case, the spindle checkpoint—the yeast two-hybrid assay helps researchers put together entire biochemical pathways and begin to understand how these proteins function together inside a cell. A

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recent twist is to use automation techniques to screen entire genomes.^[4] Every open-reading frame that encodes a protein—there are approximately 6000 in budding yeast—is fused both to the DBD and to the AD, and the two fusion libraries are screened against one another.

Now in widespread use, the two-hybrid assay has been used to identify thousands of new protein–protein interactions.^[4, 5] In response to the utility of this approach, several laboratories have begun to develop transcription-based assays that can be carried out in bacteria, or protein–protein interaction assays based on alternative readouts such as enzyme complementation or fluorescence resonance energy transfer (FRET). Moreover, the assay is being extended to the detection of other interactions. There are one-hybrid assays for detecting DNA–protein interactions, and three-hybrid assays for detecting RNA–protein and small molecule–protein interactions. A few of these advances are highlighted in this article.

In Vivo Protein–Protein Interaction Assays

While similarities in transcription among eukaryotic organisms allow the yeast two-hybrid assay to be transferred readily to mammalian cell lines, new transcription-based assays must be developed for bacteria. There are several potential advantages to working in bacteria. Generally, molecular biology techniques have been optimized in *E. coli*. Since the transformation efficiency of *E. coli* is several orders of magnitude greater than that of yeast, a larger number of protein variants can be screened. The rapid doubling time of *E. coli* would decrease the time required for the selection experiments. For several years, only the yeast two-hybrid assay was in use. Recently, however, bacterial protein–protein interaction assays have begun to be reported.^[6–9]

One approach to developing transcription-based assays in bacteria has taken advantage of the fact that many bacterial repressors and activators are dimeric proteins with structurally distinct DNA-binding and dimerization domains. Hu et al.^[6] demonstrated that the C-terminal dimerization domain of the λ -repressor could be replaced with the leucine zipper dimerization domain from the yeast transcriptional activator GCN4. The chimeric protein is stable and can functionally replace the λ -repressor in vivo, so providing immunity to superinfection by the λ -bacteriophage or efficient repression of an artificial λ -promoter and β -galactosidase reporter gene. There are other strategies for detecting protein–protein interactions in bacteria as well.^[6–9]

Alternatively, there is interest in developing assays for detecting protein–protein interactions that are not based on transcriptional activators or repressors. While the information that is known about the biochemical mechanism of transcription in eukaryotes suggests that two-hybrid assays should be able to detect weak interactions and be relatively insensitive to conformation, it may be that other types of assays are more effective. Several alternative approaches have been devised. Generally, these approaches rely either on the induced interaction of two complementary fragments of a protein to reconstitute enzymatic activity or fluorescence resonance energy transfer.^[9–13]

One such assay is based on the synthesis of adenosine 3',5'-cyclic monophosphate (cAMP) by adenylate cyclase (Figure 2).^[9] The adenylate cyclase from *B. pertussis* can be split

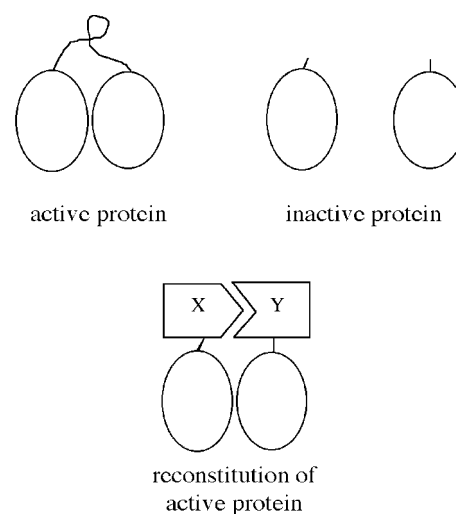


Figure 2. Protein complementation assay. A protein that carries out a detectable function is cleaved into two halves that are inactive when no longer connected. The two protein halves are fused to protein X and protein Y, respectively. If proteins X and Y bind to one another the protein's function is reconstituted.

into two functionally complementary fragments, T18 and T25, which allows protein dimerization to be assayed based on dimerization of T18 and T25 and reconstitution of adenylate cyclase activity. Adenylate cyclase is essential for the synthesis of cAMP. cAMP activates the catabolite activator protein (CAP), and the activated cAMP/CAP complex induces transcription of several genes, including the lac operon. Thus, it is possible to screen for adenylate cyclase activity using β -galactosidase plate assays or selections for growth on lactose. Ladant and co-workers^[9] have demonstrated that dimerization of the leucine zipper domain of GCN4, the N-terminal domain of tyrosyl-tRNA synthase, and the yeast splicing factors Prp11 and Prp12 can all be detected using this assay. Similar assays using reconstitution of dihydrofolate reductase (DHFR) or β -galactosidase have been described by Remy and Michnick,^[12] and Blau and co-workers,^[11] respectively. It will be interesting to see the relative merits of different assays, and there may be ways to exploit assays that show conformational dependence or other supposed weaknesses.

DNA- and RNA–Protein Interactions

Early on, it was realized that, just as the yeast two-hybrid assay could be used to detect protein–protein interactions, transcriptional activators could be used directly, in a “one-hybrid” assay, to detect DNA–protein interactions (Figure 3A). DNA-binding proteins that bind to a given target DNA sequence could be isolated from cDNA libraries encoding all of the proteins expressed in a given organism or specific cell type. Alternatively, the optimal or naturally occurring recognition sequences for a given regulatory protein could be determined. For example, with such an approach Wang and Reed cloned Olf-1, a transcriptional activator

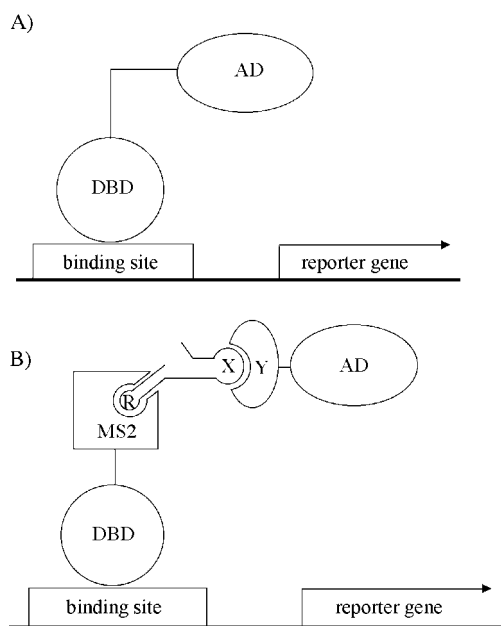


Figure 3. One- and three-hybrid assays. A) In the one-hybrid assay, the transcription activation domain (AD) is fused directly to the DNA-binding domain (DBD). This assay can be used to identify either a DBD that binds to a specific DNA sequence or the binding site for a given DBD. B) Compared with the yeast two-hybrid system, the three-hybrid system used to detect RNA–protein interactions has one additional component, a hybrid RNA molecule. One half of the hybrid RNA is a known RNA (R) that can bind the MS2 coat protein (MS2) with high affinity and serves as an anchor. The other half is RNA X, whose interaction with protein Y is being tested.

believed to be the critical switch for the coordinated expression of olfactory-specific genes.^[14] A factor had been identified previously that was expressed in nuclear extracts from the nasal epithelium but not other tissues. The difficulty was in cloning this factor and determining its sequence. An olfactory cDNA library was subcloned into a GAL4 AD plasmid to produce millions of plasmids, each expressing a different olfactory protein fused to the GAL4 AD. These plasmids were then introduced into a yeast strain that allowed the Olf-1–GAL4 fusion protein to be selected from the millions of other olfactory protein fusions by a growth selection for transcription of an essential histidine biosynthesis gene. With an entirely different purpose, Pabo and co-workers recently used a bacterial one-hybrid selection system, not for studying natural DNA–protein interactions, but to engineer a zinc finger DNA-binding protein that binds to a designed target DNA sequence.^[8]

Selecting for RNA–protein interactions is less straightforward because RNA–protein fusions cannot be generated directly *in vivo* and because routine biochemical assays that turn RNA-binding events into an amplifiable signal are not available. This difficulty was circumvented by adding a third component to the two-hybrid system and making a “three-hybrid” assay (Figure 3B).^[15, 16] The third component is a hybrid RNA molecule where one half is a well-studied RNA molecule that binds to a known protein with high affinity and the other half is the RNA molecule of interest whose protein binding partner is in question. In total, then, the three-hybrid system consists of two protein chimeras, one RNA chimera, and a reporter gene. The hybrid RNA molecule bridges the

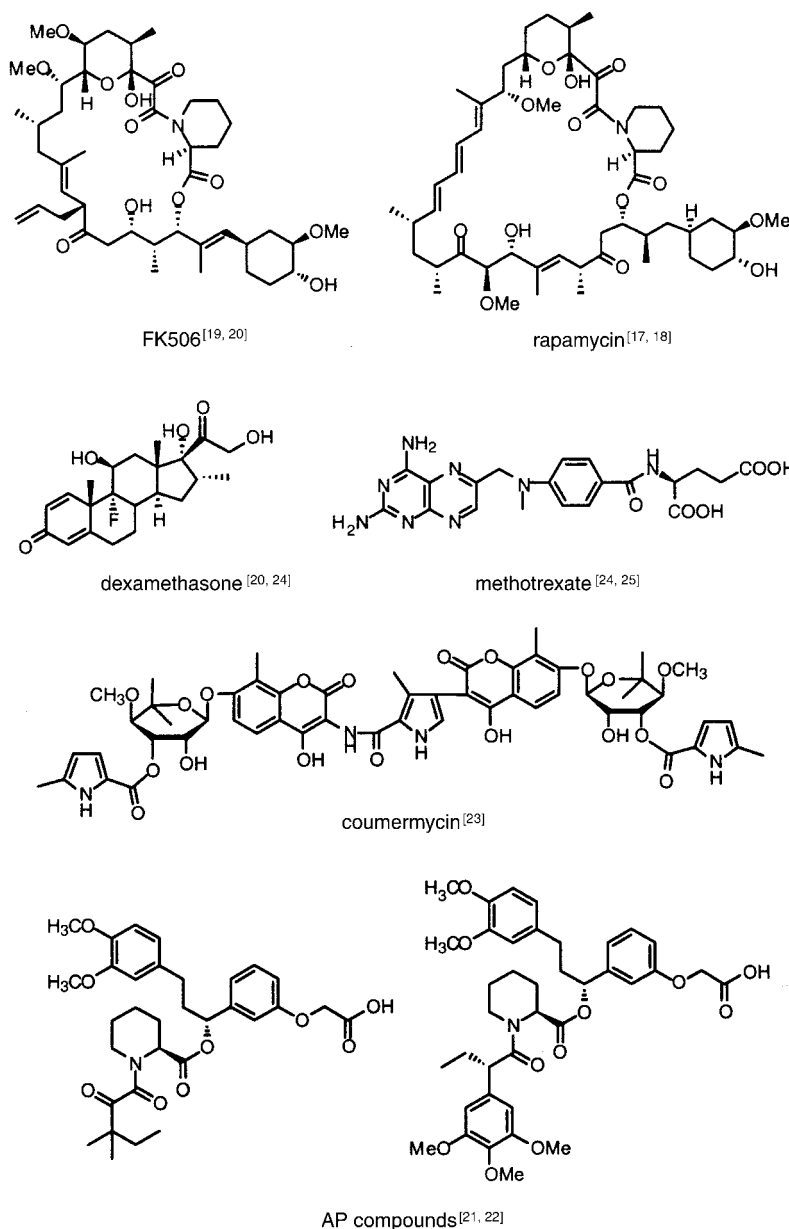
DNA-binding and activation domain fusion proteins and activates transcription of a reporter gene. Wickens and co-workers first built this three-hybrid system^[15] and then used it to identify a regulatory protein from *C. elegans* that binds to the 3′-untranslated region of the *fem-3* gene and mediates the sperm/oocyte switch in hermaphrodites.^[16]

Small Molecule–Protein Interactions

Just as an RNA molecule can be introduced to mediate the interaction between the DNA-binding and activation domains, so can a small molecule. These small molecules have often been termed chemical inducers of dimerization (CIDs). To date, both monomeric and dimeric small molecules have been employed. Stan et al.^[17] showed that the pharmacophore rapamycin could dimerize two fusion proteins, the DBD targets of rapamycin (TOR2) and the FK506/rapamycin binding protein (FKBP12)–AD, and could activate transcription of a reporter gene. This result was consistent with previous biochemical data suggesting that rapamycin acts by dimerizing TOR2 and FKBP12 *in vivo*. Furthermore, they used the transcription assay to show that the interaction requires a conserved Ser residue in TOR2, as a Ser 975 → Arg mutant of TOR2 failed to activate transcription of the reporter gene. Concurrently, a mammalian homologue of yeast TOR was identified by Chiu et al. from a mouse cDNA library using a similar transcription-based assay,^[18] which demonstrated that this modified two-hybrid system could also be used in large-scale screening and selections.

Dimeric CIDs have been used much in the same way as hybrid RNA molecules, with one half of the molecule serving as an anchor and the other half being the compound in question. The first dimeric CIDs were dimers of the immunosuppressant FK506.^[19] Licitra and Liu^[20] built what they called a “yeast three-hybrid assay” that employs two fusion proteins: the glucocorticoid receptor (GR) fused to the DNA-binding protein LexA, and FKBP12 fused to the B42 transcription activation domain. The two fusion proteins are bridged by a heterodimeric dexamethasone–FK506 molecule. Dexamethasone binds to GR with a low nanomolar dissociation constant, as does FK506 to FKBP12. The key to the success of these systems is most likely the ligand–receptor pairs, hence one major area of development is new CID pairs. Researchers at ARIAD Gene Therapeutics have developed several CIDs based on purely synthetic analogues of FK506.^[21, 22] Coumermycin, which is a naturally occurring asymmetric homodimer, has also been used as a CID.^[23] We recently reported a dexamethasone–methotrexate CID that efficiently dimerizes GR and DHFR in the yeast three-hybrid assay.^[24] The main advantage to this system is that both dexamethasone and methotrexate are readily available and that the heterodimeric derivative can be prepared readily. In addition the low picomolar affinity of methotrexate for the *E. coli* DHFR probably contributes to the efficacy of this CID. A methotrexate homodimer is being developed for use in the bacterial λ -repressor system.^[25]

In their simplest application, CIDs can be used in combination with transcription-based dimerization assays as diffusible inducers of gene transcription. There are also many



other potential applications. Licitra and Liu^[20] suggested that these systems be used to identify the cellular targets of known pharmacophores. In a proof of principle experiment using the immunosuppressant FK506, they showed that a heterodimeric dexamethasone–FK506 molecule could be used to select the natural target of FK506, FKBP12, from a Jurkat cDNA library fused to the B42 activation domain. The yeast three-hybrid assay can also serve as a tool for engineering proteins with new binding specificities. A variant of the FKBP12–rapamycin-associated protein (FRAP) that is selective for a rapamycin analogue was isolated from a library of FRB mutants by Liberles et al. using a three-hybrid assay carried out in a mammalian cell line.^[26] The FRB mutants were designed to create a new pocket in their binding sites to accommodate an additional substituent installed on rapamycin to block binding to wild-type FRB. The most selective mutant was identified by screening several FRB mutants in the three-hybrid assay.

Conclusion

The two-hybrid assay has already been used to detect thousands of new protein interactions, so what remains? One open question is whether other dimerization assays might be even more powerful than the two-hybrid assay—able to pick up lower affinity interactions or less sensitive to changes in conformation. It will be interesting to see how new *in vivo* dimerization assays fare over the next few years. There is still considerable room for optimization of the RNA or small-molecule ligand/receptor handles in the yeast three-hybrid assays to increase their sensitivity. The real question, however, is how this powerful assay can be exploited. While thousands of new protein interactions have been detected, the field is still wide open for chemists interested in understanding and manipulating biological interactions.^[8, 26] Even more intriguing, perhaps, is the possibility that this assay can be used as more than just a readout for binding interactions.^[27, 28]

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Recent Developments in Catalytic Asymmetric Strecker-Type Reactions

Larry Yet*

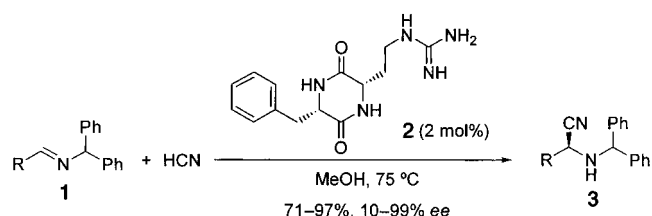
The Strecker amino acid synthesis, which involves treatment of aldehydes with ammonia and hydrogen cyanide (or equivalents) followed by hydrolysis of the intermediate α -aminonitriles to provide α -amino acids (Scheme 1), was first



Scheme 1. Classical Strecker synthesis of α -amino acids.

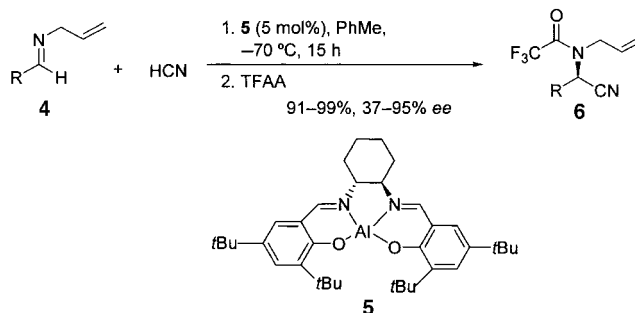
reported in 1850.^[1] This method has been applied on an industrial scale toward the synthesis of racemic α -amino acids, but more recently interest in nonproteinogenic α -amino acids in a variety of scientific disciplines has prompted intense activity in the asymmetric syntheses of α -amino acids.^[2] The catalytic asymmetric Strecker-type reaction offers one of the most direct and viable methods for the asymmetric synthesis of α -amino acid derivatives. It is the purpose of this Highlight to disclose recent developments in this emerging field of importance.

Lipton and co-workers investigated the viability of the asymmetric Strecker amino acid synthesis in which they utilized cyclic guanidine dipeptide **2** in the reaction of *N*-benzhydrylimines **1** with hydrogen cyanide to give *N*-benzhydryl- α -aminonitriles **3** (Scheme 2).^[3] *N*-Benzhydrylimines **1**, derived from aromatic aldehydes, gave products **3** in generally high enantiomeric excess. However, electron-deficient 3-nitro, 3-pyridyl, and aliphatic aldehyde derivatives afforded racemic products.



Scheme 2. Asymmetric Strecker synthesis with cyclic dipeptide **2** (Lipton and co-workers).

Sigman and Jacobsen reported the first example of a metal-catalyzed enantioselective Strecker-type reaction using a chiral Al^{III} –salen complex (salen = *N,N'*-bis(salicylidene)-ethylenediamine dianion).^[4] A variety of *N*-allylimines **4** were evaluated in the reaction catalyzed by complex **5** to give products **6**, which were isolated as trifluoroacetamides in good yields and moderate-to-excellent enantioselectivities (Scheme 3). Substituted arylimines **4** were the best substrates,



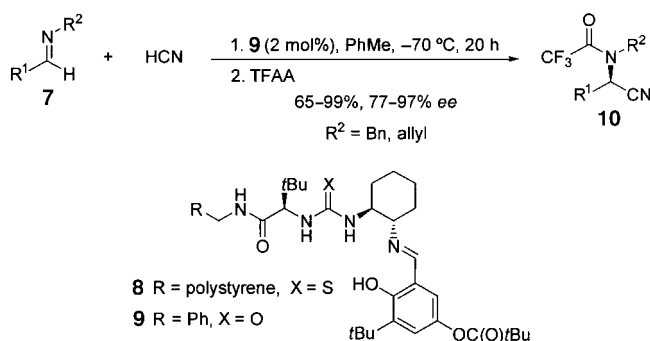
Scheme 3. Asymmetric Strecker synthesis with chiral Al^{III} –salen catalyst **5** (Sigman and Jacobsen). TFAA = trifluoroacetic anhydride.

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while alkyl-substituted imines afforded products with considerably lower *ee* values. Jacobsen and co-workers also reported that non-metal Schiff base catalysts **8** and **9** proved to be effective in the Strecker reaction of imines **7** with hydrogen

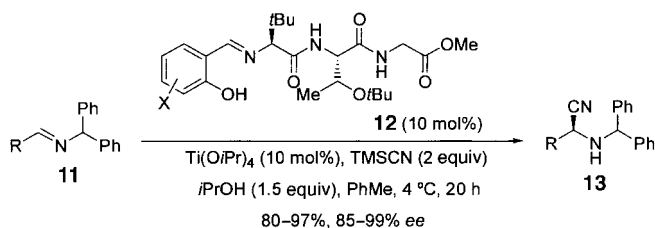
cyanide to afford trifluoroacetamides **10** after reaction with trifluoroacetic anhydride, since the free amines were not stable to chromatography (Scheme 4).^[5]



Scheme 4. Asymmetric Strecker synthesis with salicylimine catalyst **9** (Vachal and Jacobsen). Bn = benzyl.

Catalyst **9** was very effective for the hydrocyanation of both aromatic and aliphatic imines **7** in high enantioselectivities and yields, and either *N*-benzyl- or *N*-allylimines could be used. The key elements responsible for the high enantioselectivity were the presence of bulky *tert*-butyl substituents at both the amino acid position and at the 3-position of the salicylimine moiety. Resin-bound catalyst **8** allowed purification of the Strecker products by simple filtration and solvent removal, and the catalyst could be reused indefinitely without loss of either activity or enantioselectivity. Recently, Vachal and Jacobsen have applied catalyst **9** to keto-imines in the presence of hydrogen cyanide in the catalytic synthesis of quaternary α -carbon atoms.^[6]

Snapper, Hoveyda and co-workers employed a similar salicylimine Schiff base ligand **12** in the asymmetric titanium-catalyzed Strecker reaction of aromatic *N*-benzhydrylimines **11** to give addition products **13** (Scheme 5).^[7] It was found that



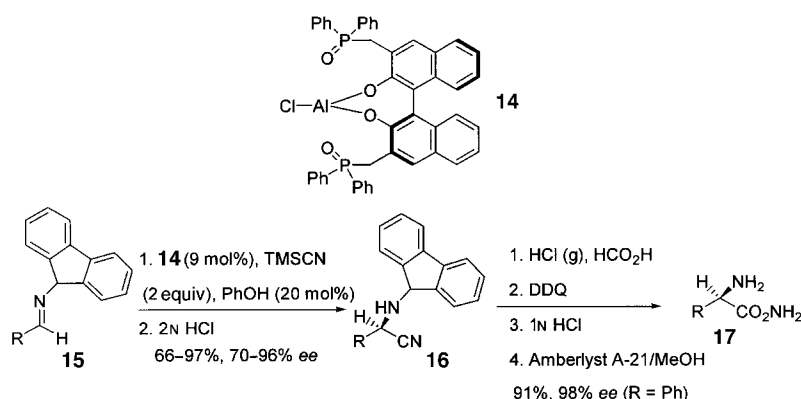
Scheme 5. Strecker synthesis with the chiral Schiff base ligand **12** (Snapper, Hoveyda, and co-workers). TMS = trimethylsilyl.

catalyst turnover was facilitated significantly in the presence of 2-propanol as an additive. The aminonitriles **13** are stable and directly purified by chromatography (acylation is not needed) and can be readily converted into the corresponding amino acids with 6*N* HCl by concomitant cyanide hydrolysis and amine deprotection.

Shibasaki and co-workers disclosed a general asymmetric Strecker-type reaction that was controlled by bifunctional

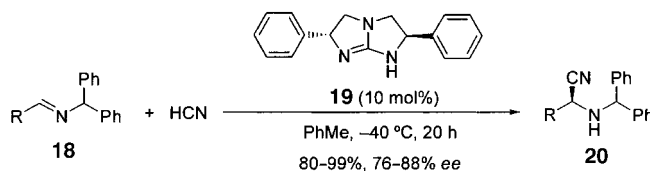
Lewis acid–Lewis base catalyst **14**.^[8] *N*-Fluorenylimines **15** underwent catalytic asymmetric Strecker-type reactions with binaphthol catalyst **14** to give α -aminonitriles **16** in good to excellent enantioselectivities and yields (Scheme 6). α -Aminonitrile **16** (*R* = Ph) could then be converted into α -amino-amide **17** in several steps. Aromatic, aliphatic, heterocyclic, and α,β -unsaturated imines **15** were used as general substrates in these reactions. The origin of the highly enantioselective catalysis by **14** is believed to be attributed to the simultaneous activation of imines and trimethylsilyl cyanide by the Lewis acid and the oxygen atom of the phosphane oxide, respectively. With this catalyst system, *N*-allyl- and *N*-benzhydrylimines generally gave lower enantioselectivities. The addition of phenol was found to have a beneficial effect on the reaction rates.

Corey and Grogan recently developed a novel catalytic enantioselective Strecker reaction which utilized the readily



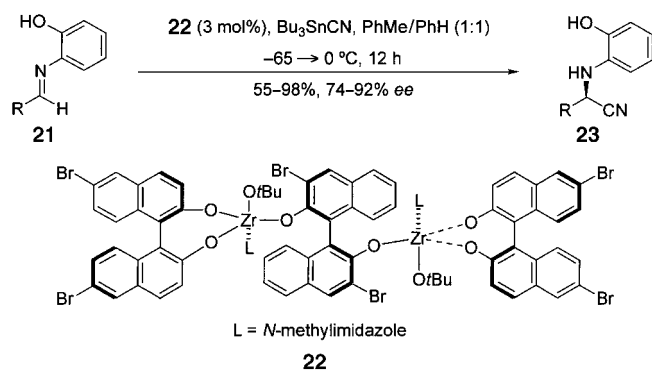
Scheme 6. Asymmetric Strecker synthesis with the bifunctional Lewis acid–Lewis base catalyst **14** (Shibasaki and co-workers). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

available chiral C_2 -symmetric guanidine **19** as a bifunctional catalyst.^[9] The addition of hydrogen cyanide to achiral aromatic and aliphatic *N*-benzhydrylimines **18** gave *N*-benzhydryl- α -aminonitriles **20** (Scheme 7), which were readily converted into the corresponding amino acids with 6*N* HCl. The use of *N*-benzyl- or *N*-fluorenylimines afforded products of poor enantiomeric purity.



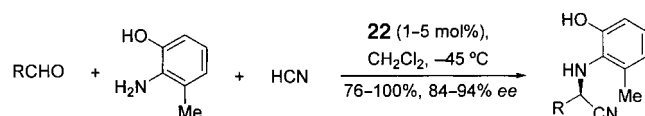
Scheme 7. Asymmetric Strecker synthesis with the chiral guanidine catalyst **19** (Corey and Grogan).

Kobayashi and co-workers employed the chiral zirconium binuclear catalyst **22** in the asymmetric Strecker-type synthesis of α -aminonitriles **23** from aldimines **21** with tributyltin cyanide (Scheme 8).^[10] Aldimines **21** were in turn derived from aliphatic, aromatic, and heterocyclic aldehydes. High levels of enantioselectivities were observed in these reactions.



Scheme 8. Asymmetric Strecker synthesis with the chiral zirconium binuclear catalyst **22** (Kobayashi and co-workers).

These α -aminonitriles could be converted into α -amino acid derivatives by methylation of the phenolic hydroxyl group, followed by acid or base hydrolysis and oxidative cleavage with cerium ammonium nitrate. Furthermore, the catalytic asymmetric Strecker amino acid synthesis starting from achiral aldehydes, amines, and hydrogen cyanide using catalyst **22** has been achieved (Scheme 9). It is noted that



Scheme 9. Three-component Strecker synthesis with the chiral zirconium binuclear catalyst **22** (Kobayashi and co-workers).

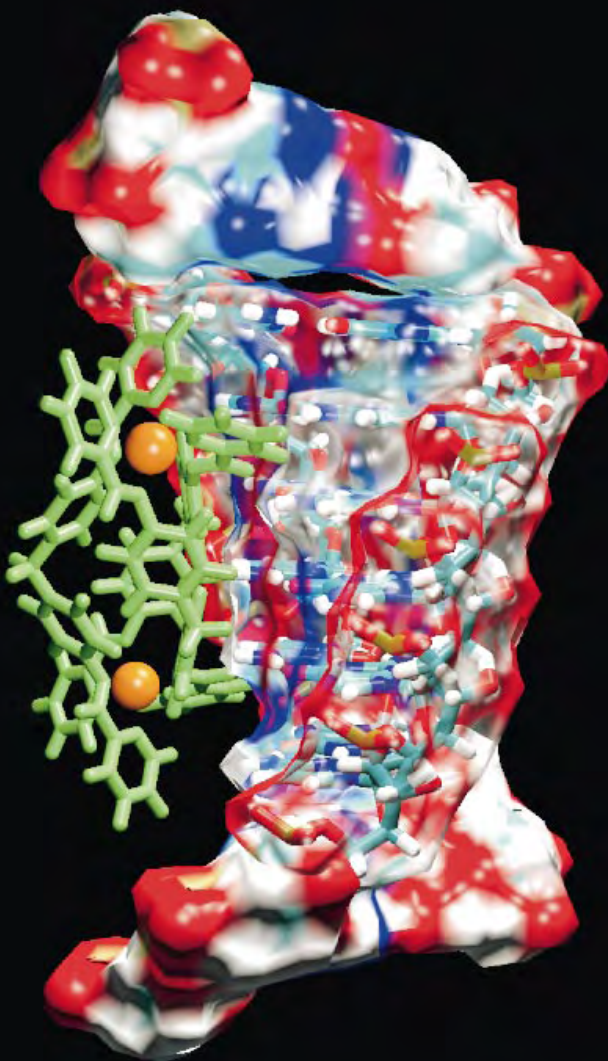
150 years after the first discovery of the Strecker reaction, a truly efficient three-component asymmetric version has been accomplished.^[10b] While the use of tributyltin cyanide is suitable for laboratory-scale experiments, industrial applica-

tions are expected for a more benign three-component catalytic asymmetric Strecker process using hydrogen cyanide.

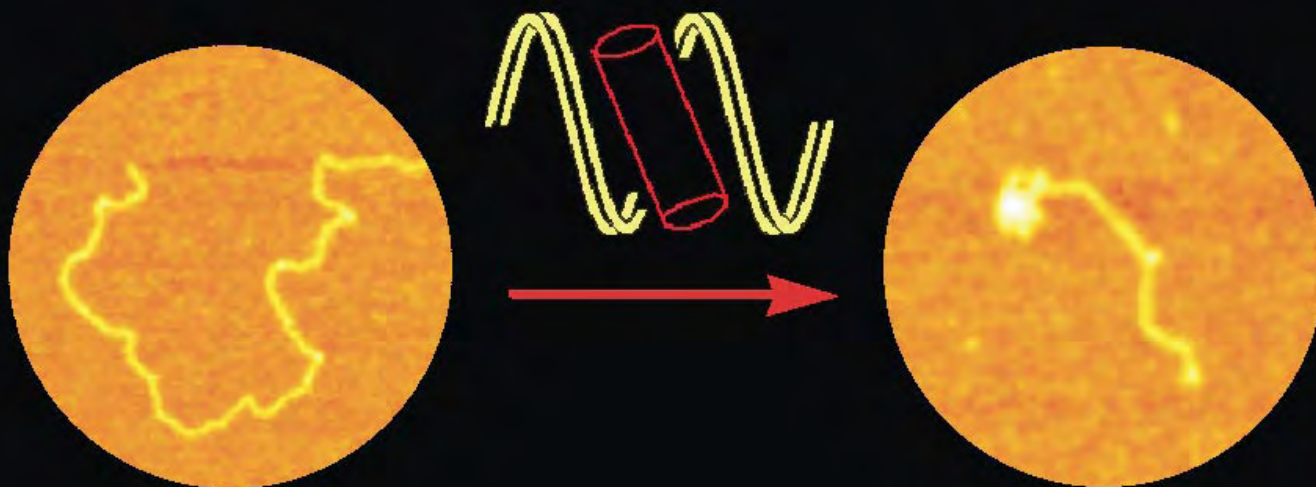
This Highlight has shown that catalytic asymmetric Strecker-type reactions are possible but are still under active investigation for improvements and generalizations. Important areas for future study will include wider application of starting aldimine substrates, finer catalyst tuning, and of the simple conversion of α -aminonitriles into α -amino acid derivatives. More importantly, large-scale industrial applications of these methods to the production of optically active α -amino acids will be the ultimate goal of these investigations.

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Supramolecular methodology allows the design of cylindrical DNA-binding agents of similar dimensions to protein DNA-recognition motifs. The synthetic cylinders target the major groove of DNA, often the preferred site for natural recognition, and induce intramolecular DNA coiling, a remarkable structural effect not observed with conventional small synthetic DNA binders.



More information see the following pages.



Intramolecular DNA Coiling Mediated by a Metallo-Supramolecular Cylinder**

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While DNA encodes the essential blueprint for life, within biological systems its structure and function is regulated by proteins. These macromolecules frequently achieve DNA recognition by binding in or around its major groove since the size and shape of the major groove of B-DNA varies most with base sequence. For example, transcriptional regulators often involve cylindrical binding units, such as alpha helices or zinc fingers, that insert into the major groove and may bend or kink the DNA.^[1, 2] Such protein recognition of DNA contrasts with synthetic small-molecule recognition agents, which being smaller than proteins, tend to target the minor groove^[3] or act by intercalation^[4] and often cause little or no bending of the DNA. Some small polycations, such as spermine, do cause significant DNA bending, resulting in *intermolecular* DNA toroids^[5] (this interaction may involve a major-groove component^[6]). By way of contrast, in cells, DNA forms tightly compacted *intramolecular* nucleosome core particles by looping, in a series of kinks,^[7] around cationic histone proteins.^[8] We have designed a metallo-supramolecular cylinder^[9, 10] whose size and shape is comparable with a protein zinc finger and herein report a quite unexpected result: that these cylindrical units “wrap up” individual DNA duplexes in an *intramolecular* fashion, which is unprecedented with traditional small-molecule DNA condensation agents.

Supramolecular chemistry provides methodology for the design of large synthetic arrays. We reasoned that supramolecular assembly would allow us to bridge, synthetically, the size gap between traditional small-molecule and larger biomolecule DNA-recognition motifs. We have recently

described how synthetic tetracationic supramolecular cylinders (with a triple helical architecture) may be readily prepared through interaction of metal ions with imine-based ligands ($[M_2L_3]^{2n+}$, where n is the charge on each metal, Figure 1).^[9, 10] Modelling indicated that these cylinders are the

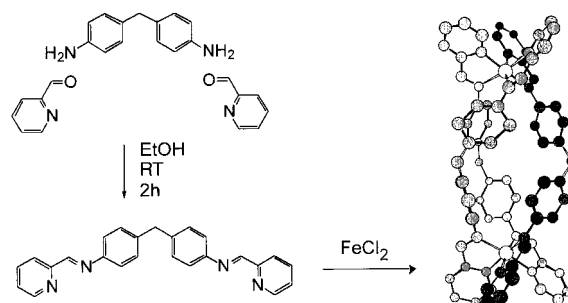


Figure 1. The molecular structure of the ligand and the tetracationic triple helical supramolecular cylinder $[Fe_2(C_{25}H_{20}N_4)_3]Cl_4$.

correct size and shape to fit into the B-DNA major groove spanning five base pairs (bp), but are too large to bind in the minor groove (analogous to protein major-groove recognition motifs^[2]). Because of their dimetallic nature, the cylinders also have a high positive charge that should enhance their binding to the negatively charged DNA. We have therefore probed the binding of these supramolecular cylinders to DNA.^[11]

Circular dichroism (CD, the difference in absorption of left and right circularly polarized light) is sensitive only to the asymmetry or chirality of a system.^[12] Thus, with racemic $[Fe_2L_3]^{4+}$ in the presence of DNA, the observation of a CD signal in the optical transitions of $[Fe_2L_3]^{4+}$ indicates that it is binding to the DNA. The induced CD (ICD) spectra (Figure 2b) show that $[Fe_2L_3]^{4+}$ is interacting with the DNA in a single binding mode, which is consistent with major groove binding, when the ligand concentration is below a DNA–bp:cylinder ratio of ~5:1. Above this concentration a change in behavior is observed.^[22] The DNA-region CD spectrum is not perturbed significantly at low cylinder loadings suggesting that the DNA geometry is not significantly perturbed. As DNA CD is dominated by local interactions of the bases^[12] this implies that any structural perturbations induced by the cylinders do not displace the ligands significantly from their nearest neighbor relative orientations.

Long polymers, such as DNA, can be oriented by the viscous drag created by the rotation of one cylinder inside another. The extent of orientation may be assessed using linear dichroism (LD, the difference in absorption of light polarized parallel and perpendicular to an orientation axis).^[12, 13] B-DNA base pairs are oriented approximately perpendicular to the DNA helix axis,^[14] which is also the orientation axis, and thus the base $\pi-\pi^*$ transitions give a negative LD signal. If a molecule is bound to DNA in a specific orientation, it will also be oriented by the viscous drag and so exhibit LD signals. If the molecule is free/unbound or bound in a random orientation, then no LD signal is observed for its transitions. For both the low and high loadings of the supramolecular cylinder on DNA, an $[Fe_2L_3]^{4+}$ LD signal is

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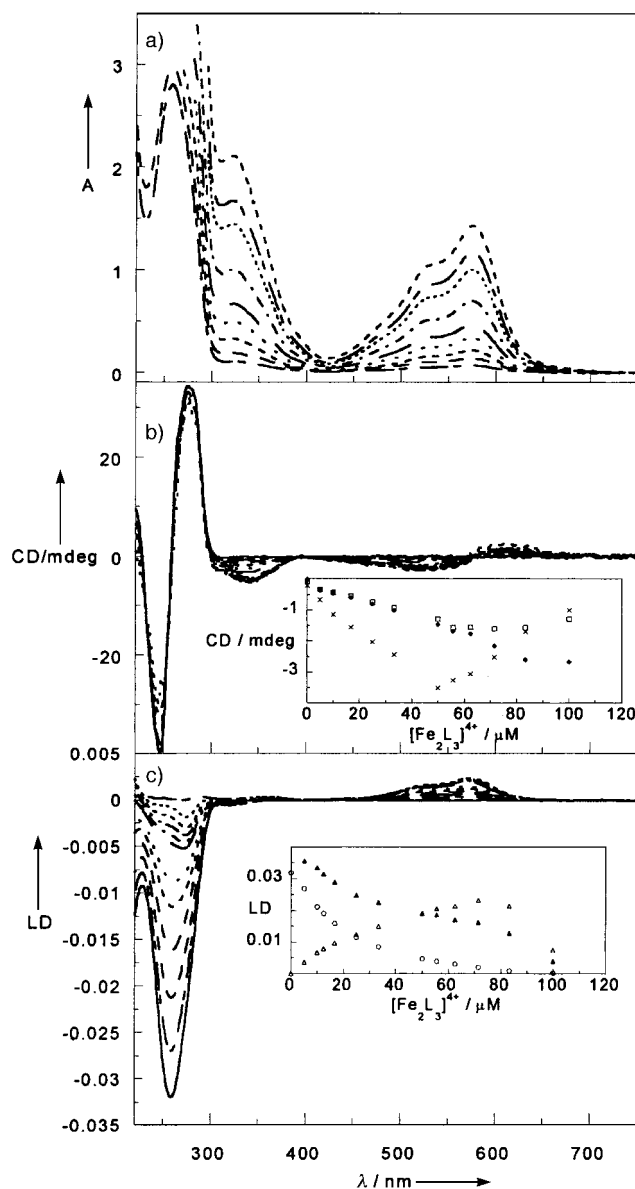


Figure 2. a) Absorbance (1 cm pathlength), b) CD (1 cm pathlength), and c) LD (1 mm pathlength) of 500 μM (in bases) calf thymus DNA (Sigma) in 20 mM NaCl and 1 mM $\text{Na}(\text{CH}_2)_2\text{AsO}_2 \cdot 3\text{H}_2\text{O}$ buffer (pH 6.8) with increasing concentrations of $[\text{Fe}_2\text{L}_3]^{4+}$. The DNA base: $[\text{Fe}_2\text{L}_3]^{4+}$ ratios are for smallest magnitude spectra to largest at 550 nm: 2.5:1, 3:1, 3.5:1, 4:1, 4.5:1, 5:1, 7.5:1, 10:1, 15:1, 25:1, and 50:1. Inserts show CD or LD at key wavelengths as a function of $[\text{Fe}_2\text{L}_3]^{4+}$ concentration. Insert wavelengths are: $\times$ CD at 315 nm; $\square$ CD at 375 nm; $\blacklozenge$ CD at 541 nm; $\circ$ LD at 258 nm; $\triangle$ $10 \times$ LD at 568.5 nm; $\blacktriangle$ $500 \times$ LD divided by $[\text{Fe}_2\text{L}_3]^{4+}$ concentration at 568.5. The 568 nm LD data divided by the $[\text{Fe}_2\text{L}_3]^{4+}$ concentration is shown to illustrate the different orientations of the cylinder-bound DNA and the average DNA. The solid line corresponds to DNA without any $[\text{Fe}_2\text{L}_3]^{4+}$.

observed (Figure 2c), confirming its DNA-binding is not random. More importantly, the DNA LD signal arising from the bases is significantly reduced on addition of even very low concentrations of the supramolecular cylinder (at these loadings the 260 nm LD signal can be completely ascribed to the DNA LD). This could result from either an increase in DNA flexibility or a shortening of the DNA by kinking, bending, compaction, or aggregation. The CD (Figure 2b) confirms that the double-stranded B-DNA structure is

retained and that the local structure is not significantly perturbed suggesting that kinking is not the reason for DNA shortening. The insert to Figure 2c shows that the 580 nm molar $[\text{Fe}_2\text{L}_3]^{4+}$ LD signal per molecule decreases more slowly than the DNA signal; this is consistent only with shortening of the DNA through bending.

The extent of shortening can be determined empirically and the results are summarized in Table 1. There is a significant reduction in the average DNA length when $[\text{Fe}_2\text{L}_3]^{4+}$ is present. It is possible then to estimate the bend angles induced per cylinder to achieve this average length reduction (Table 1). Although such bend-angle calculations are only approximate, it is apparent that at low cylinder loading, there is more effect per cylinder than at high loadings. A bend of $45 \pm 15^\circ$ per cylinder may be estimated, with the higher values being at lower cylinder loadings (Table 1).

Table 1. The effective length of DNA and approximate average bend, $\langle \theta \rangle$, induced per molecule of $[\text{Fe}_2\text{L}_3]^{4+}$ to achieve the observed shortening of DNA in solution; n is the number of ligands bound per persistence length^[20] of DNA to the nearest whole number. The value of n is overestimated by ~ 1 for the higher ligand loads where the persistence length is reduced (see Figure 3). The values in parentheses indicate what would follow for smaller n . Below a bp:cylinder ratio of 7.5:1 the cylinder contributes more than 20% of the absorbance intensity at 258 nm.

Ligand:DNA Ratio	$-\text{LD}^r$ (258 nm) ^[a]	$L^{\text{lig}}/L^{\text{free}}$	n	$\langle \theta \rangle$ ^[b]
1: ∞	0.09667	1.00		
1:100	0.08182	0.87	2	60°
1:50	0.06455	0.71	3	55°
1:40	0.05758	0.64	4 (3)	45° (60°)
1:30	0.04879	0.56	5 (4)	40° (50°)
1:20	0.03485	0.41	7 (6)	35° (40°)
1:15	0.02591	0.31	9 (7)	30° (40°)

[a] The relationship between LD signal and B-DNA length for long DNAs has been found empirically to follow the formula^[21] $\text{LD}^r = \frac{\text{LD}}{A} = -\frac{k_1 G}{k_2 + G}$ where A is the absorbance and G , the velocity gradient of the flow cell, is constant in our experiments, $k_1 = 0.42$ for our experiment (from Figure 8 of ref. [21]), and the inverse of $1/k_2$ is proportional to the DNA length.

From ref. [21] it therefore follows that $\frac{L^{\text{lig}}}{L^{\text{free}}} = \frac{1 + \frac{k_1}{\text{LD}^{\text{free}}}}{1 + \frac{k_1}{\text{LD}^{\text{lig}}}}$ where L is the length of DNA, and "lig" and "free" denote in the presence and absence of the ligand respectively. [b] θ is determined by assuming that the DNA bends are additive, so bend the DNA into a planar circle (rather than a zigzag for which L^{lig}/L would be independent of binding ratio). If n is even then $\frac{L^{\text{lig}}}{L} = \frac{2}{n}(\frac{1}{2} + \cos(q) + \dots + \cos(\frac{n-1}{2}q))$, if n is odd then $\frac{L^{\text{lig}}}{L} = \frac{2}{n}(\cos(\frac{q}{2}) + \dots + \cos((n-1)\frac{q}{2}))$. Thus θ calculated is the minimum bend per molecule.

To obtain a molecular-level picture of the binding, we have acquired atomic force microscopy (AFM) tapping-mode images of the ligand with a "random" sequence linearized plasmid DNA (Figure 3b–d). At low loading the effect of the cylinders appears to be to increase the average bend angle and number of bends in the DNA compared with the free DNA (Figure 3a), thus reducing the inter-bend distance; consistent with the LD experiments there is a fairly uniform distribution of bound cylinders. The most striking feature of the images is the intramolecular coiling of the DNA at moderate cylinder loadings (Figure 3c). A level of cooperativity is apparent in the coiling process, with some fully coiled strands observed in the presence of uncoiled (but bent) DNAs.

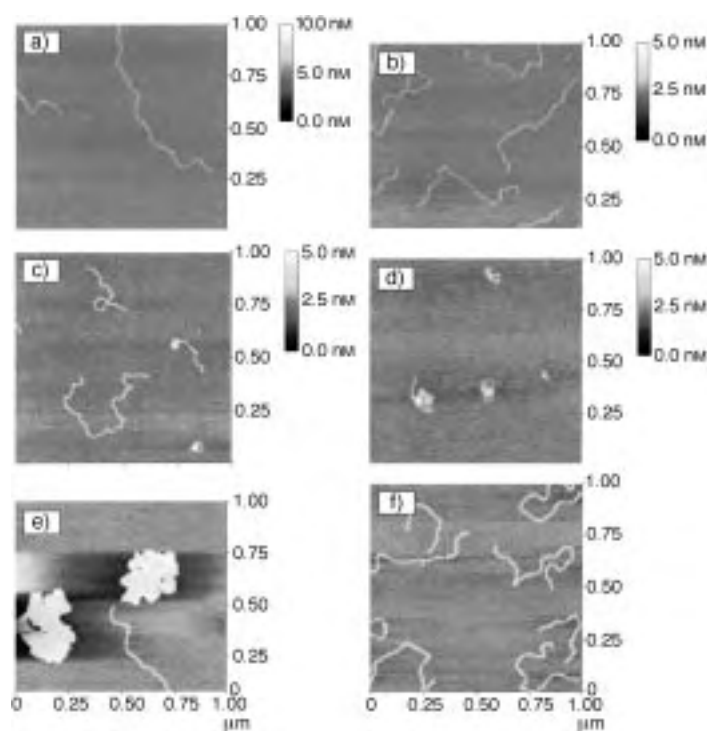


Figure 3. AFM images of linear plasmid DNA (pBR322, 4361 bp, diameter of 475 nm, cleaved with PstI and SalI enzymes to give two linear fragments of 1401 bp and 2962 bp) with the following metal complexes (DNA:metal complex ratio given in parentheses): a) free DNA, b) low $[\text{Fe}_2\text{L}_3]^{4+}$ concentration (10:1), c) medium $[\text{Fe}_2\text{L}_3]^{4+}$ concentration (10:3), d) high $[\text{Fe}_2\text{L}_3]^{4+}$ concentration (10:5), e) $[\text{Co}(\text{NH}_3)_6]^{3+}$, and f) $[\text{Ru}(\text{phen})_3]^{2+}$.

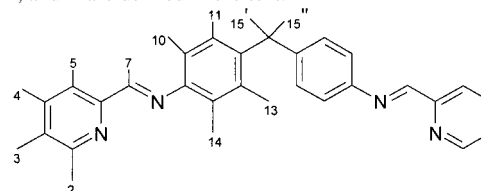
AFM images of metal complexes bound to DNA are rare and mainly restricted to the covalent binding of drugs such as *cis*-platin.^[15] Therefore to investigate whether these unusual observations were common to AFM images of other non-covalent DNA-binding metal complexes or arose as a result of the larger size, larger charge, and cylindrical shape of our metallo-supramolecular cylinder we analyzed a set of controls under the same conditions. Two well-studied metal complexes with different binding characteristics were selected; $[\text{Co}(\text{NH}_3)_6]^{3+}$ is a known DNA condensation agent and has been shown by LD to bend DNA.^[10] By contrast, $[\text{Ru}(\text{phen})_3]^{2+}$ (selected as a “spherical” model for half of $[\text{Fe}_2\text{L}_3]^{4+}$; phen = 1,10-phenanthroline) does not cause DNA condensation and has comparatively little bending effect, though the Δ enantiomer does reduce the DNA orientation in flow-LD experiments.^[16, 17] The cobalt complex condenses and aggregates the DNA into intermolecular clusters (Figure 3e). Again the binding appears to be cooperative with clusters observed in the presence of uncoiled DNA strands. With $[\text{Ru}(\text{phen})_3]^{2+}$ no *inter* or *intramolecular* packaging was observed, simply an increase in the average size and number of DNA bends (Figure 3f). These images are very similar to those previously reported for $[\text{Ru}(\text{phen})_3]^{2+}$ with *p*BluBacHisb DNA.^[18] The effect of $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ (*cis*-platin), which covalently binds to DNA mainly in a G–G intrastrand mode that bends the DNA by about 45°,^[19] is again distinct from the effect of the cylinder showing larger average bends and shorter links between the bends.

The interaction between a double-helical DNA oligonucleotide, 5'-d(GACGGCCGTC)₂, and $[\text{Fe}_2\text{L}_3]^{4+}$ has also been studied by 1D and 2D NMR spectroscopy to determine the local aspects of the geometry of the binding. A number of nuclear Overhauser enhancement spectroscopy (NOESY) cross-peaks representing contacts between the duplex $[\text{Fe}_2\text{L}_3]^{4+}$ confirm binding in the major groove (Table 2 and Figure 4).^[23] Though this does not preclude other binding

Table 2. Intermolecular NOEs between the helicate and d(GACGGCCGTC)₂. The numbering scheme used is illustrated below.

Helicate protons	Chemical shift [ppm]	Nucleic acid protons
S1 H7	8.74	C7B H2'(vw), G5A NH(m), G5A H8(w), C6A NHF(m)
S1 H11	6.25	C6A H5(s), C6A H6(w), C6A NHF(m), C6A NHB(m), G5A NH(m), G5A H8(m)
S1 H13	5.34	C6A H5(m)
S1 H14	4.06	G5A NH(s)
S2 H2	8.33	C6A H2'(w), C6A H2''(m), G5A NH(m)
S2 H3	8.24	C6A H2'(vw), C6A H2''(w), G5A NH(m)
S2 H7	8.84	C6A H2'(w), C6A H2''(m), G5A NH(s), G5A H8(w)
S2 H10	5.19	G4A H3'(w)
S2 H11	6.33	C6A H2'(w), G4A H8(vw), G5A H8(w), G5A NH(m), C6B H5(m), C7B H5(m)
S2 H14	4.28	G5A NH(m)
S3 H2	8.39	G5A NH(m)
S3 H11	6.53	C6B H5(s)
S4 H2	8.32	C7B H2'(w), C7B H2''(m), C6B H6(m), C7B H6(m)
S4 H7	8.53	G5A NH(s), C6B H6(w), C7B H6(w)
S4 H11	6.32	C6B H6(m), C7B H6(m)
S4 H14	3.90	G5A NH(s)

S1–S4, A, and B are defined in the text.



modes at either higher cylinder loadings or that are undetectable by NMR spectroscopy. We observed four different binding positions (in the major groove) of the helicate indicated in Table 2 by S1–S4. The symmetry of the palindromic oligonucleotide is changed upon addition of the helicate. We observed two sets of signals for the residues C3–G8 (indicated in Table 2 by A and B). When viewed down the groove (third view in Figure 4) contact between $[\text{Fe}_2\text{L}_3]^{4+}$ and the base of the groove is apparent. The driving force for helix bending observed in the LD and AFM images can easily be envisaged. Nuclear Overhauser effect (NOE) restrained molecular-docking and molecular dynamics calculations are in progress to determine the extent of duplex bending induced by the supramolecular cylinder. Further details of the NMR spectroscopy including NOESY and total correlation spectroscopy (TOCSY) spectra are included in the Supporting Information.

In conclusion, we have shown that supramolecular methodology can be used to design DNA-binding motifs of a similar

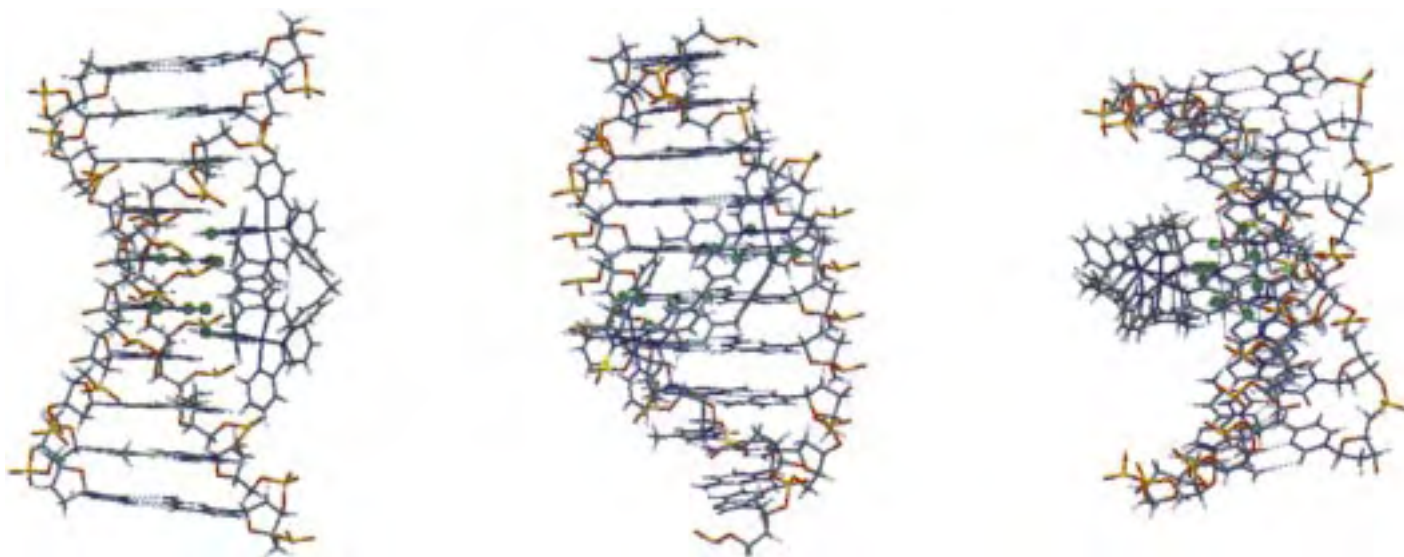


Figure 4. Views of $[\text{Fe}_2\text{L}_3]^{4+}$ docked into the major groove of $[5'\text{-d}(\text{GACGGCCGTC})_2]$ based on NMR experiments. A number of NOESY cross-peaks representing contacts, indicated by circles, between the duplex $[\text{Fe}_2\text{L}_3]^{4+}$ confirms binding in the major groove.

scale to those found in nature. These large binding motifs can lead to remarkable effects on DNA structure, as observed by CD, LD, and AFM. Intermolecular NOEs between the complex and DNA confirms that the cylinder binds to DNA in the major groove. There may also be other NMR-silent binding modes. We are currently assessing the extent to which this approach can be extended with new supramolecular arrays designed to achieve specific structural effects in a sequence specific fashion. The topic of DNA structure control by proteins, and, by extension, synthetic analogues, is of particular relevance in the light of the ongoing quest to understand not only the coding inherent in DNA, but how it is processed or may be suppressed in biosystems.

Experimental Section

Absorbance spectra were collected using a Jasco V-550 UV/Vis absorption spectrometer. CD and LD spectra were collected using a Jasco J-715 spectropolarimeter adapted for LD measurements. The LD samples were oriented in a radial couvette flow cell.^[28]

AFM images of linear plasmid DNA (pBR322, 4361 bp, diameter of 475 nm, cleaved with PstI and SalI enzymes to give two linear fragments of 1401 bp and 2962 bp) were collected with a range of metal complexes. DNA–metal complex adducts were prepared as follows: digested pBR322 DNA (15 ng) was incubated in an appropriate volume with the required metal complex in 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES) buffer (HEPES 4 mM pH 7.4, KCl 5 mM, and MgCl_2 2 mM). All solutions were made with water (18.2 M Ω) filtered through 0.2 nm FP030/3 filters (Schleicher & Schuell GmbH, Germany) and centrifuged at 4000 g several times to avoid salt deposits and provide a clear background when they were imaged by AFM. The samples were left to equilibrate at 37 °C for 5 h in the dark. Samples were prepared for AFM by placing a drop (6 μL) of DNA solution or DNA–metal complex solution onto Ni-treated green mica (Ashville–Schoonmaker Mica Co., Newport New, VA). After adsorption for five minutes at room temperature, the samples were rinsed for 10 s in a jet of deionized water (18 M Ω cm $^{-1}$ Milli-Q water) directed onto the surface with a squeeze bottle. The samples were blow dried with compressed argon over silica gel and then imaged using a Nanoscope III Multimode AFM (Digital Instrumentals Inc., Santa Barbara, CA) operating in tapping mode in air at a scan rate of 1–3 Hz. The AFM probes were 125 μm -long monocrystalline silicon cantilever with integrated conical

shaped Si tips (Nanosensors GmbH, Germany) with an average resonance frequency of 330 kHz and spring constant $K = 50 \text{ N m}^{-1}$. The cantilever is rectangular and the tip radius given by the supplier is 10 nm with a cone angle of 35° and high aspect ratio. The images were obtained at room temperature ($T = 23 \pm 2^\circ\text{C}$) and typical relative humidity of >55 %. Four different samples from each reaction were imaged in several places and many times to obtain reliable measurements. The persistence length (the length over which the average deflection of the helix axis is one radian (57.3°)) for each DNA was determined by assuming the DNA is flat on the surface of the mica and converting the segment lengths to base pairs (bp) by dividing by 0.36 nm. This value will be a lower bound as it is a projection of the length onto a plane. The average bend is determined by summing successive bends until a value greater than 57°, then recording the length and bend obtained. This value will be an upper bound because of the projection issue. The values of these average parameters are approximately: 120 bp/67° for free DNA; 92 bp/69° wrapped into intramolecular bundles with $[\text{Fe}_2\text{L}_3]^{4+}$; 92 bp/70° with $[\text{Ru}(\text{phen})_3]^{2+}$; 114 bp/68° condensed with $[\text{Co}(\text{NH}_3)_6]^{3+}$; and 80 bp/80° with cisplatin.

NMR spectra were recorded on a Bruker DRX 600 MHz instrument using a 2.8 mm sample of the oligonucleotide purchased from Oswel DNA Service. The sample was purified with ion-exchange chromatography, desalted, and paramagnetic impurities were removed using a Chelex column. The oligonucleotide was then dissolved in 90 % H_2O and 10 % D_2O containing 50 mM phosphate buffer and 40 mM NaCl. The pH of the sample was 6.9. $[\text{Fe}_2\text{L}_3]^{4+}$ was added in five steps to reach a 1:2 ratio. This ratio was selected so that no precipitation should occur. A combination of through space nuclear Overhauser effect (NOESY) and through bond correlated (TOCSY) two-dimensional spectra were recorded. The spectra were recorded at 17 °C using Double Pulsed Field Gradients Spin Echo water suppression (dpfgsew5).^[25, 26] The data were processed using XWIN-NMR (Bruker) and analyzed using Sparky.^[27] The imino protons were clearly observed indicating that the double-helical geometry was retained. TOCSY experiments were performed to facilitate the assignment procedure and clearly show the double sets of signals for the central residues of the DNA. A number of cross-peaks in the NOESY map represent proton–proton contacts between the oligonucleotide and $[\text{Fe}_2\text{L}_3]^{4+}$ as shown in Table 2. Molecular docking was performed using the DOCK 4.0.1 suite of programs.^[24] A grid was constructed on the basis of the NOE contacts. The grid spacing was 0.2 Å and the sampling size was 10000 structures. The 30 best results were then energy minimized.

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Unique Single-Atom Binding of Pseudohalogeno Ligands to Four Metal Ions Induced by Their Trapping into High-Nuclearity Cages**

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High-nuclearity transition metal clusters continue to attract a great deal of interest, partly because of their fascinating physical properties and partly for the beauty and complexity of their structures. An interesting subarea of transition metal cluster chemistry is the small but growing family of molecules that, in their ground states, have unusually large numbers of unpaired electrons. Molecular clusters with very high spin values have been prepared, often by one-pot synthesis, with the highest values to date being $S_T = 51/2$ for the recently reported^[1] Mn₉^{II}Mo₆^V cyano-bridged system and $S_T \approx 33/2$ for one of the clusters in a compound containing cocrystallized Fe₁₇ and Fe₁₉ species.^[2] The large-spin ground state results from either ferromagnetic (or ferrimagnetic) exchange interactions between the paramagnetic centers and/or topologically frustrated antiferromagnetic interactions.^[3] In addition, it has recently become apparent that a fairly large S_T value is a necessary (but not sufficient) requirement for molecules to be able to exhibit the new phenomenon of single-molecule magnetism.^[4] The synthesis of new high-spin molecules is thus of interest. However, it is difficult to predict in advance what type of topology and structure will lead to a high-spin cluster and even more difficult to then achieve a rational synthesis of such a species.

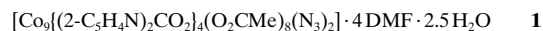
In most polynuclear clusters, magnetic exchange interactions are mainly propagated by bridging OH[−], OR[−], O^{2−}, or RCO₂[−] ligands, or a combination of two or more of these groups; often these interactions lead to antiferromagnetic coupling. An alternative attractive approach to increase the S_T ground state would be the replacement of one or more of the above-mentioned bridging ligands with other groups that are more prone to ferromagnetic coupling. Herein we describe our preliminary results demonstrating the application of this approach.

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We have successfully applied a strategy to the antiferromagnetic cluster $[\text{Co}_9\{(2\text{-C}_5\text{H}_4\text{N})_2\text{CO}_2\}_4(\text{O}_2\text{CMe})_8(\text{OH})_2]$ ($(2\text{-C}_5\text{H}_4\text{N})_2\text{CO}_2^{2-}$ is the doubly deprotonated *gem*-diol form of di-2-pyridyl ketone, $(2\text{-C}_5\text{H}_4\text{N})_2\text{CO}$),^[5] in which, while maintaining the thermodynamically stable Co_9 cage skeleton, we have been able to modulate the superexchange pathway by substitution of the μ_4 -hydroxides by unprecedented μ_4 -azide or μ_4 -cyanate ligands. The magnetic response changes from antiferromagnetic interactions for NCO^- to a ferrimagnetic high-spin anisotropic system in the N_3^- case.

Reaction of $\text{Co}(\text{O}_2\text{CMe})_2 \cdot 4\text{H}_2\text{O}$ with $(2\text{-C}_5\text{H}_4\text{N})_2\text{CO}$ and NaN_3 (9:4:2 molar ratio) in hot DMF led to a dark blue solution from which the nonanuclear cage **1** was isolated. The



X-ray crystal structure analysis^[6] of **1** (Figure 1) reveals that the nine Co^{II} atoms adopt a topology of two square pyramids

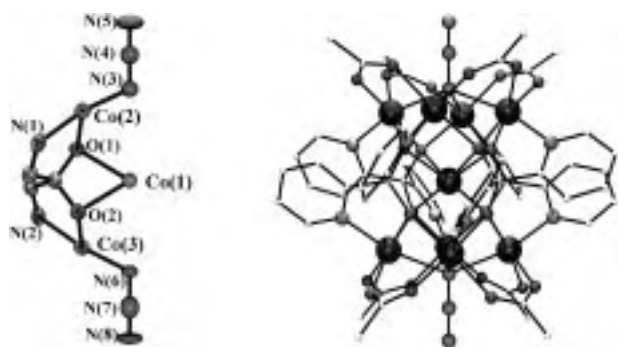
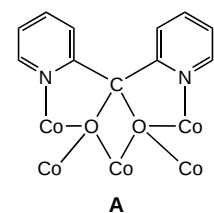


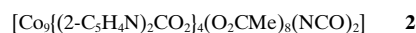
Figure 1. Left: Labeled asymmetric unit of **1**. Right: A view of cage **1**; the size of carbon atoms has been reduced for clarity and the solvate molecules are not shown. Selected bond lengths [Å] and angles [°]: Co(2)-N(3) 2.378(1), Co(3)-N(6) 2.362(1); Co(2)-N(3)-Co(2)' 83.06(6), 139.3(2)°, Co(3)-N(6)-Co(3)' 83.38(5), 140.3(2), O(1)-Co(1)-O(2) 75.85(4).

sharing a common apex (Co(1)). The oxygen atoms of the $\mu_5:\eta^1:\eta^3:\eta^3:\eta^1-(2\text{-C}_5\text{H}_4\text{N})_2\text{CO}_2^{2-}$ ligands (**A**) are placed in the center of the triangular faces of the pyramids, and bridge the central cobalt atom with two Co^{II} atoms of the base of each pyramid. A salient feature of the structure is the coordination number eight around Co(1), which is extremely rare in Co^{II} chemistry.^[7] Each $\text{Co} \cdots \text{Co}$ edge of the bases is further bridged by one *syn,syn*- $\mu_2:\eta^1:\eta^1$ -acetate group; each base is capped by



one μ_4 -azido end-on ligand. The MeCO_2^- ligands create a concave cavity (the diameter of which is determined by the crown of the acetate ligands) on the base of each pyramid, into which the linear azido ligand is effectively trapped (Figure 2).

A similar reaction performed by using NaOCN instead of NaN_3 allows easy isolation of the analogous cyanate cage **2**,



which has also been characterized by single-crystal X-ray crystallography.^[6] Its structure is remarkably similar with the

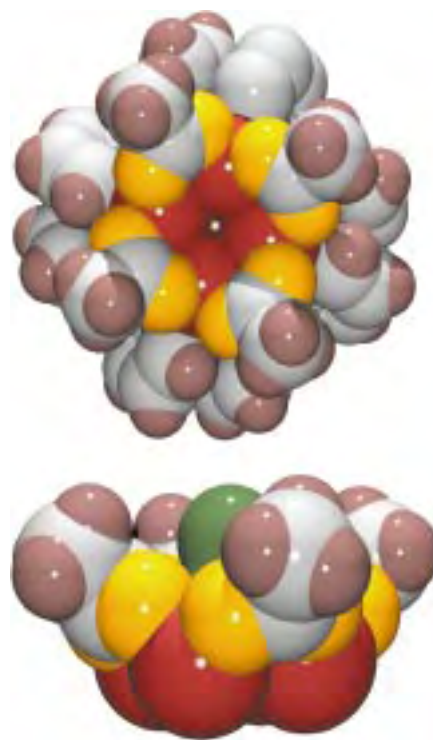


Figure 2. Axial view of the anion-trapping cavity (top) and a view showing one azide ligand in the cavity (bottom). Color code: Co: red, O: orange, N: green, C: gray, H: brown.

structure of **1** and contains μ_4 end-on (through the N atom) cyanate ligands.

As might be expected, the analogous nonanuclear clusters with angular monoanionic ligands, for example NO_2^- , or even with monoatomic but bigger anions such as Cl^- or Br^- , cannot be obtained. Our results indicate a good anion-trapping selectivity of the nonanuclear cage for small linear anions involving Lewis acid–base interactions. In fact, the Co_9^{II} cluster can be considered as a (preformed) host capable of accommodating external anionic ligands such as N_3^- and OCN^- .

For the azide ligand, the μ_2 coordination mode is common, while the μ_3 one is quite unusual.^[8] For the cyanate ligand even the $\mu_{1,1}$ end-on (through the N atom) coordination mode is rare. To the best of our knowledge, compounds **1** and **2** are unprecedented examples of μ_4 end-on coordination of pseudohalogeno ligands. They also extend the small number of structurally characterized polynuclear 3d metal complexes with mixed $(2\text{-C}_5\text{H}_4\text{N})_2\text{CO}_2^{2-}/\text{RCO}_2^-$ ligation.^[5, 9]

For complex **1** the product $\chi_{\text{M}}T$ increases from $23.38 \text{ cm}^3 \text{ K mol}^{-1}$ to a maximum of $25.29 \text{ cm}^3 \text{ K mol}^{-1}$ at 16 K, and then decreases to $19.73 \text{ cm}^3 \text{ K mol}^{-1}$ at 2 K, whereas on cooling, $\chi_{\text{M}}T$ for **2** decreases continuously from 25.95 down to $10.15 \text{ cm}^3 \text{ K mol}^{-1}$ at 2 K (Figure 3). The weak minimum $\chi_{\text{M}}T$ at 116 K for **1** is the ferrimagnetic signature of the antiferromagnetic coupling between the central Co^{II} atom and the two ferromagnetically coupled squares in the bases of the cage. Magnetization measurements in the $\pm 5 \text{ T}$ range of the external field do not show hysteresis, and ac measurements show neither an out-of-phase signal nor frequency dependence of the susceptibility, which excludes single-molecule magnet behavior for the two complexes. The strong aniso-

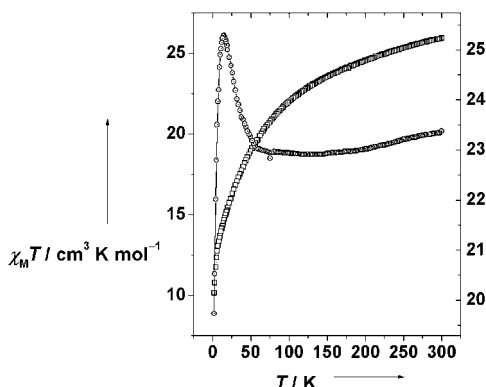
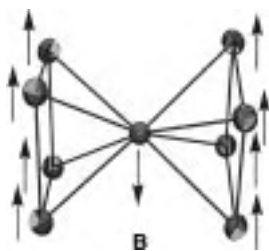


Figure 3. Plots of $\chi_M T$ versus T for complexes **1** (right y axis, dot centered circles) and **2** (left y axis, open squares).

trophy of the Co^{II} ion does not permit us to quantify the magnitude of the coupling constants, but a qualitative approach to the interaction pattern may be deduced from the above data. Complex **2** shows an overall antiferromagnetic coupling, which may be associated to dominant antiferromagnetic coupling in the Co^{II} squares of the cage (Co_4 partial $S=0$) giving an S_T value equivalent to one isolated local spin. In contrast, the data for compound **1** should be associated to ferromagnetic coupling mediated by the μ_4 -azido bridges, giving an S_T value of seven times that of the local spins (assuming antiferromagnetic coupling between $\text{Co}(1)$ and $\text{Co}(2)$, and between $\text{Co}(1)$ and $\text{Co}(3)$) and leading to a ferrimagnetic system **B**.



One of the main findings of this work is the experimental evidence that the end-on azide bridges introduce specifically ferromagnetic components in the superexchange scheme of a cage compound. The azide ligand in the end-on coordination mode is an effective bridging ligand which quasi-systematically affords ferromagnetic coupling between two, three, and now four metal ions for a large range of M-N-M bond angles.^[10] Accordingly, the end-on azide ligand is a good substitute for hydroxo bridges in clusters to increase the S value of the ground state. However the most important result of this work is the novel coordination mode observed for N_3^- and OCN^- , which is induced by their effective trapping in the positively charged cavities of the Co_9 cage.

Experimental Section

DMF (25 mL) was added to a mixture of $\text{Co}(\text{O}_2\text{CMe})_2 \cdot 4\text{H}_2\text{O}$ (0.15 g, 0.6 mmol), $(2\text{-C}_3\text{H}_4\text{N})_2\text{CO}$ (0.06 g, 0.32 mmol), and NaN_3 (0.02 g, 0.30 mmol). The solids dissolved on stirring under heating to give a dark blue solution, which was allowed to stand undisturbed at room temperature for 3 days. Well-formed, X-ray quality pink-red crystals of **1** appeared, which were isolated by filtration, washed with DMF and Et_2O , and dried in air. Yield 60%. A similar procedure was employed to isolate complex **2** using NaOCN instead of NaN_3 . The two complexes gave satisfactory elemental analyses ($\text{C}, \text{H}, \text{N}$).

Magnetic susceptibility data were collected with a Quantum Design SQUID magnetometer in the temperature range 2–300 K. The output data

were corrected for the diamagnetism of the samples and the sample holder. Magnetization measurements were performed in the ± 5 T range of the magnetic field.

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Evidence for the Existence of the McMillan Phase in a Binary System of a Metallomesogen and 2,4,7-Trinitrofluorenone**

Torsten Hegmann, Jens Kain, Siegmur Diele, Gerhard Pelzl, and Carsten Tschierske*

The design of soft matter, well organized at different length scales is a topic of interdisciplinary research which is important for both materials science and life science. Such materials include block copolymers, surfactant aggregates, colloidal systems, and liquid crystals. Layer structures such as lamellar phases of detergent–solvent systems and smectic liquid crystals appear to be quite simple and belong to the best known and most investigated states of soft matter. Interest has focused again on these systems in light of the recent discovery of rather complex new types of supramolecular organization with interesting new properties. For example, macroscopic polar order and spontaneous chiral symmetry breaking have been realized with achiral banana-shaped molecules organized in liquid layers.^[1]

Nearly three decades ago a quite unusual layer structure was predicted theoretically.^[2] In addition to the well-known subgroups of smectic phases, such as SmA and SmC (see Figure 1 a and b, respectively), a biaxial smectic phase with

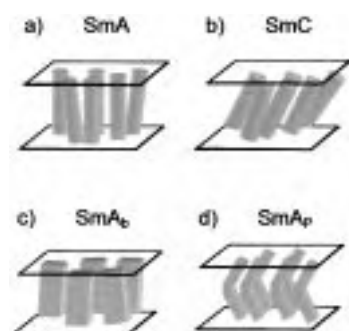


Figure 1. Schematic representation of a section of one layer of a) a smectic A (SmA) phase, b) a smectic C (SmC) phase (in the SmC phase the molecules in the adjacent layers have the same tilt direction (synclinal interlayer correlation), in the SmC_A subtype the tilt direction alternates from layer to layer (anticlinal interlayer correlation)), c) a biaxial smectic (SmA_b) phase, built up by orthogonally arranged boardlike molecules (McMillan phase, C_M), and d) a possible arrangement in a smectic A phase with polarization (SmA_p) within the layers.

orthogonally aligned molecules in the layers should exist. In contrast to the well-known SmA phase, in which the molecules can freely rotate around their long axes and which therefore is optically uniaxial, in this new phase the molecules should have a preferred direction within the layer planes

(SmA_b, see Figure 1 c) leading to an optical biaxiality of this orthogonal phase.^[3] This new phase is associated with a reduction of the symmetry from $D_{\infty h}$ (SmA) to D_{2h} (SmA_b). Further possible variants of packing can occur in the case of banana-shaped molecules for which the packing of the molecules can lead to a polarization within the layers (Figure 1 d).^[1]

de Gennes suggested calling the biaxial smectic A phase (SmA_b) the C_M phase, where M stands for McMillan.^[2] Brand, Cladis, and Pleiner have predicted the properties of this special phase.^[4] Accordingly, a Schlieren texture comprising exclusively two-brush disclinations (defects of the strength $S = \pm 1/2$; two dark brushes meet at the disclination points, see, for example, Figure 2 b) should be observed by microscopy

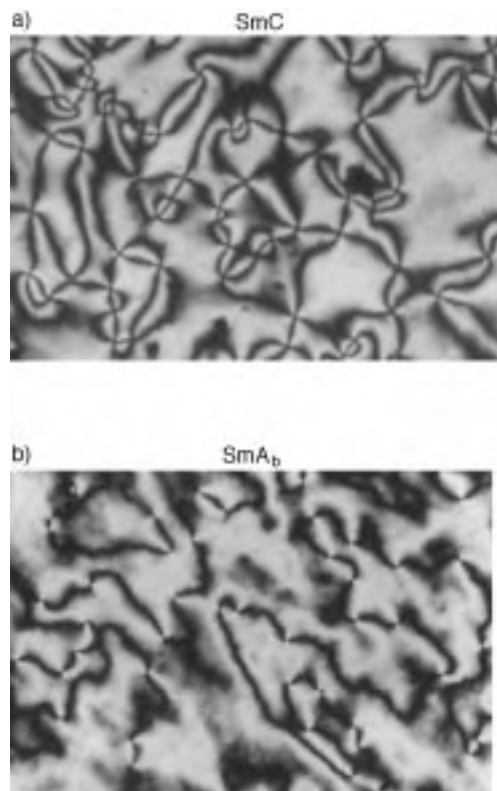


Figure 2. Schlieren textures of a) the SmC phase of **1** at 108 °C and b) the SmA_b phase of the **1**/TNF mixture at 120 °C in the homeotropically aligned regions (crossed polarizers).

between crossed polarizers. Many attempts have been made to realize such a nontilted biaxial smectic mesophase in practice. This phase can be expected to occur for molecules with a pronounced boardlike (sanidic) shape, and there have been two reports in which such SmA_b phases were observed conoscopically after alignment of the materials in a magnetic^[5] or an electric field;^[6] however, in both cases, for the nonaligned samples, the textural pictures revealed uniaxial SmA phases.^[5, 6]

Herein we report the first example of a McMillan phase that shows the predicted textural characteristics of this phase together with an orthogonal alignment of the molecules within the layers as proven by X-ray diffraction studies. In contrast to earlier reported SmA_b phases, in our case this organization is formed spontaneously in the absence of external fields.

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This new phase occurs in binary systems consisting of the metallomesogens **1–3**^[7, 8] and the electron acceptor 2,4,7-trinitrofluorenone (TNF, m.p. 175 °C).^[9] The transition temperatures of compounds **1–3** and of their binary systems with TNF are given in Table 1. The system **1**/TNF, as a representative example, was investigated in more detail.

The binary phase diagram of the **1**/TNF system is shown in Figure 3. In the contact region between **1** and TNF, the SmC phase and the SmA phase of the pure compound are drastically destabilized. At a TNF concentration of about 4–6 mol % a new phase is induced (M), which is continuously stabilized until the TNF concentration reaches 60 mol %, whereafter the stability strongly decreases again.^[10] Between crossed polarizers, this induced phase M occurs with a typical fan-shaped texture (Figure 4 a, left-hand side), interrupted by

Table 1. Phase transition temperatures of the pure compounds **1–3**^[8] and their mixtures with TNF^[a] as determined by polarized light optical microscopy.^[a]

Compound	R ¹	R ²	Pure compounds <i>T</i> [°C]	<i>T</i> _{max} [°C] with TNF ^[b]
1	H	H	K 113 SmC 117 SmA 133 Iso	SmA _b 178 M 210 Iso
2	OC ₁₀ H ₂₁	H	K 117 (SmA 101) Iso	SmA _b 162 M 179 Iso
3	OC ₁₀ H ₂₁	OC ₁₀ H ₂₁	K 115 Iso	SmA _b 128 M 165 Iso

[a] Abbreviations: K = crystalline solid, SmC = smectic C phase, SmA = smectic A phase, SmA_b = optically biaxial smectic A phase (McMillan Phase, C_M), M = induced mesophase with the typical texture of a SmA phase, Iso = isotropic liquid. [b] The maximum temperatures for the transitions SmC_M–M and M–Iso, as obtained by investigation of the contact regions between compounds **1–3** and TNF are given. They can, however, occur at different TNF concentrations (see Figure 3).

extended regions in which the molecules are homeotropically aligned. These areas are optically isotropic and appear completely black between crossed polarizers. Hence, this phase M shows the typical textural features of a SmA phase, and because this phase M is separated from the SmA phase of the pure compound **1** by an isotropic liquid region it is incompatible with the latter and therefore a different structure is expected.

In the following we focus our interest on a new phase found at lower temperature and at a TNF content of at least about 20 mol %. At the transition into this low-temperature phase only a change of the birefringence can be detected in the region with the fan-shaped texture (see Figure 4 a, right-hand side). In the homeotropically aligned regions the transition can be seen by the formation of a striped pattern (see Figure 4 b)^[11] which immediately turns into a Schlieren texture (see Figure 2 b). The low-temperature phase cannot

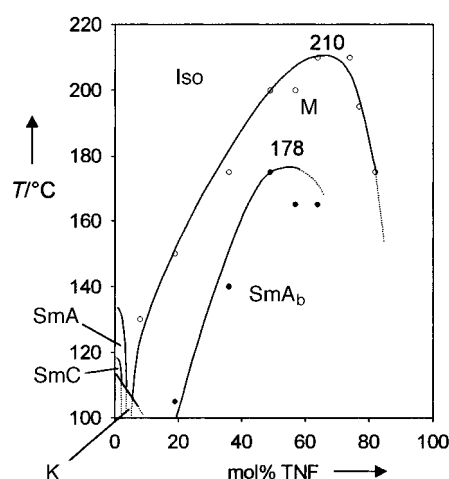


Figure 3. Simplified binary phase diagram of the **1**/TNF system. Broad biphasic regions (at ca. 20 K) were found for the transition from the induced M phase to the isotropic liquid state (Iso). Only the upper temperature limits of these biphasic regions are shown in the phase diagram; for the abbreviations, see footnote [a] in Table 1.

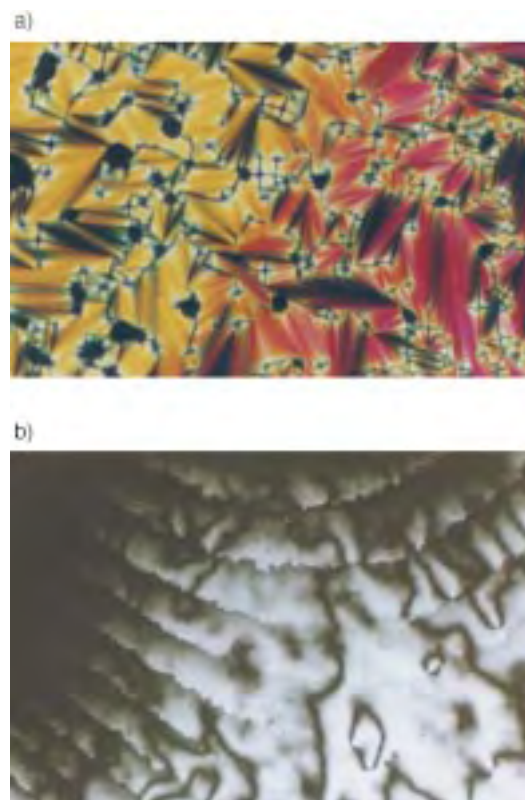


Figure 4. Transition from the induced high-temperature mesophase M to the SmA_b phase in the **1**/TNF mixture as seen between crossed polarizers at 140 °C: a) in regions with a fan-shaped texture (M: yellow fans at the left-hand side, SmA_b: red fans at the right-hand side), b) in the homeotropically aligned regions of the induced phase (M: dark area at the left-hand side, SmA_b: birefringent texture at the lower right-hand side) with the typical stripe pattern occurring directly at the transition.

be homeotropically aligned, which indicates that this phase should be optically biaxial. Thus, the SmC phase of the pure compound and the induced low-temperature phase are optically biaxial phases and both have Schlieren textures. However, exclusively four-brush disclinations (*S* = ± 1) can be

found in the SmC phase of pure **1** (see Figure 2a), whereas exclusively two-brush disclinations ($S = \pm \frac{1}{2}$) were found in the induced phase of the mixed system (see Figure 2b). Hence, both phases should be quite different, but most importantly, the textural features of the induced low-temperature phase (Schlieren texture with two-brush disclinations and fan-shaped texture) exactly match with the textural features predicted theoretically for the SmA_b phase (McMillan phase).^[4]

To investigate the induced mesophases in more detail, X-ray scattering experiments with the pure compound **1** and with a defined mixture of compound **1** and TNF (**1**:TNF = 2:1; phase sequence SmA_b 140 M 180 Iso) have been performed by using the Guinier film method and by investigation of well aligned monodomains with a two-dimensional detector.

The X-ray diffraction pattern of the pure compound **1** (Guinier film method) is typical for conventional SmA and SmC phases. One sharp reflection is found in the small-angle region with $d = 2.94$ nm at 130 °C (SmA phase) and with $d = 3.04$ nm at 112 °C (SmC phase).^[12] Additionally, in both phases a diffuse scattering is observed in the wide-angle region. In contrast, the X-ray diffraction pattern of the induced mesophases occurring in the binary mixture is more complicated. The pattern of the nonoriented samples of the low-temperature phase display sharp reflections with instrumentally limited line shapes at $q_1 = 2\pi/2.8$ nm⁻¹, $q_2 = 2q_1$, and $q_3 = 3q_1$ ($T = 130$ °C). This indicates that this phase has a well-defined layer structure with a layer thickness of 2.8 nm at 130 °C and 2.7 nm at 170 °C. Beside these reflections four diffuse scattering maxima of weak intensity appear at $q_4 = 2\pi/1.08$ nm⁻¹, $q_5 = 2\pi/0.68$ nm⁻¹, $q_6 = 2\pi/0.47$ nm⁻¹, and $q_7 = 2\pi/0.34$ nm⁻¹. The pattern, obtained by investigation of monodomains^[13] of this phase is shown in Figure 5a. It displays preferred directions of the scattering. The scattering with q_1 , q_2 , and q_3 is positioned at the meridian, and the scattering with q_4 and q_7 is directed perpendicular to these, indicating additional electron density modulations perpendicular to the layer normal. The scattering with q_7 corresponds to 0.34 nm, a value typical for the face-to-face distance in aromatic π -stacking systems. It has a rather small full width at half maximum, indicating a rather well-defined parallel alignment of the flat molecules. The position of the scattering at the equator of the pattern proves that the aromatic parts of the molecules are aligned parallel to the layer normal, although optical biaxiality is observed. The scattering with $q_4 = 2\pi/1.08$ nm⁻¹ can be related to the width of the aromatic cores of the molecules **1** (1.1 nm according to CPK models). It is very diffuse, indicating that this electron density modulation is only of short-range order. The diffuse scattering with q_6 does not show any preferred direction and can be attributed to the average distance between the highly disordered alkyl chains (0.47 nm). The diffuse scattering with q_5 is of very low intensity and could be detected by the Guinier film method only. The latter may be due to the mean distance between short-range ordered fluctuating clusters built up between **1** and TNF molecules (0.68 nm).

Hence, all experimental findings confirm that the low-temperature phase of the binary mixture **1**/TNF should have the structure shown in Figure 6b. It is a layer structure built up

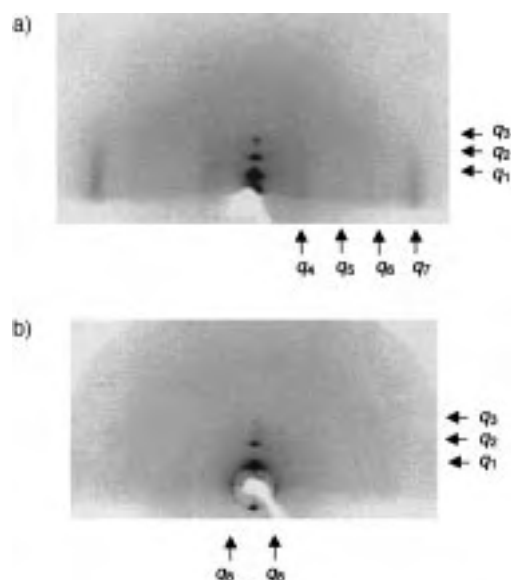


Figure 5. Two-dimensional (2D) X-ray diffraction pattern of a monodomain of the **1**/TNF mixture at 30 °C (a) and at 175 °C (b).

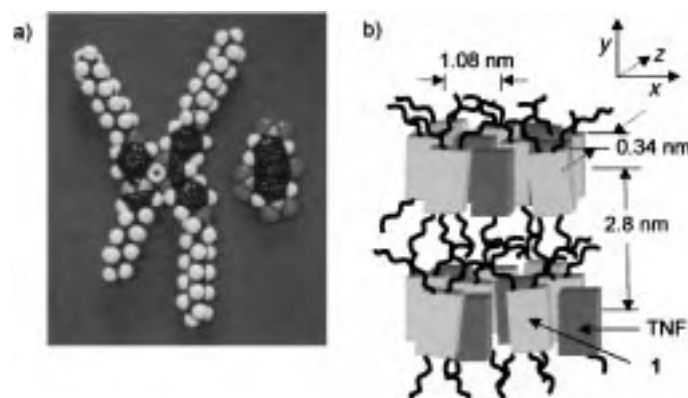


Figure 6. Arrangement of the molecules in the SmA_b phase of the mixed system **1**/TNF: a) CPK models of molecule **1** and TNF, b) proposed organization of the molecules in the SmA_b phase (corresponds to Figure 1c).

by flat molecules arranged parallel to each other and orthogonal to the layer planes. Within the layers the molecules have two different degrees of positional order. In one direction (z) there is a rather well-defined face-to-face organization of the molecules, whereas in the other direction (x) only short-range positional order is found. In other words, this phase has exactly that structure which has been suggested for the McMillan phase.^[14, 15] Remarkably, despite the rather high degree of order, this phase is highly fluid similar to conventional SmA and SmC phases.

The X-ray diffraction pattern changes a little in the high-temperature phase (M). Again, the scattering with $q_1 - q_3$ is observed at the meridian (Figure 5b). Also the diffuse scattering with q_6 resulting from the liquidlike chains remains. The intensities of the scattering with q_4 , q_5 , and q_7 decrease with increasing temperature and could not be detected with the 2D detector. Only by the film method and with sufficiently long exposure time was the very weak and smeared out scattering with q_4 and q_7 observed. These findings resemble

those discussed for the so-called $D_{ho}-D_{hd}$ transitions,^[16] for which the parallel packing of disclike molecules in columns gets lost. In the case under discussion the decrease in the intensity corresponds to the increase of the rotational disorder within the layers around the axes parallel to the layer normal, that is the orientational order of the molecules within the layers is reduced which leads to the loss of optical biaxiality. However, striking is the (reproducible) appearance of a spotlike reflection nearly perpendicular to the layer normal at the transition to the high-temperature phase. The appearance of this reflection implies a periodicity perpendicular to the layer normal. Thus, because reflections with higher or mixed Millers indices [(20) or (11)] cannot be observed and because the d value of the additional peak corresponds with the length of the molecules (equal with the period along the meridian), we assume that the additional reflection is caused by molecular rotational disorder around an axis perpendicular to the flat molecular planes. This suggests a lamellocolumnar structure of this mesophase,^[17] but further studies are necessary to exclude other possibilities.

In summary, the results of texture observations and the X-ray diffraction studies reported provide experimental proof for the theoretically predicted biaxial smectic A phase (McMillan phase). In contrast to earlier reported SmA_b phases this special molecular organization is obtained spontaneously, without previous alignment in an external field.^[18] The fan-shaped texture indicates a layer structure. The existence of a Schlieren texture proves the biaxiality of the phase, whereas the X-ray pattern of oriented samples prove the orthogonal arrangement of flat molecules in layers. The strong face-to-face packing of the molecules within the layers, indicated by an electron-density wave perpendicular to the layer normal, provides additional confirmation of the biaxiality.

Notably, compound **1** itself has the molecular shape necessary for the formation of the SmA_b phase, but the rotation around the molecular long axis is fast, so that only an uniaxial SmA phase can be observed. However, in mixed systems with a sufficiently large TNF concentration the attractive face-to-face interactions between TNF and the flat aromatic cores of compounds **1** strongly reduce the molecular rotation around the long axis, leading to the biaxiality. We suggest that attractive face-to-face attraction could also lead to biaxial nematic phases if the formation of a layer arrangement could be suppressed. Finally it should be mentioned that the dimensions of the TNF molecules fit perfectly with the dimensions of the sublayers of the aromatic core regions of the metallomesogen **1** in the smectic phases (see Figure 6b). This could additionally contribute to the stabilization of this special phase structure over a quite large concentration and temperature region.

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Multilayer Formation on a Curved Drop Surface**

Jun Bai Li,* Yi Zhang, and Ling Long Yan

The adsorption behavior of single components in emulsion systems such as proteins or phospholipids at air/water or liquid/liquid interfaces can provide information on the kinetics and interfacial activity.^[1] The development of new techniques has made it possible to extend these studies to multicomponent systems at liquid/liquid interfaces.^[2] This is particularly interesting for food emulsion systems where a colloidal droplet is often immersed into another liquid phase. The interfacial properties of milky emulsions are governed by, for example, β -lactoglobulin; these emulsions are often thermodynamically unstable.^[3] Thus the addition of the low molecular weight surfactants such as phospholipids interact with the adsorbed protein layer at the interface and thus function as a stabilizer or an emulsifier.^[1] Such a model system can be created by using the pendent drop technique, in which a solution of α -dipalmitoylphosphatidylcholine (DPPC) in chloroform was pumped through a tube to the tip of a Teflon capillary, which was immersed in an aqueous β -lactoglobulin solution. The behavior of two components from different sides of the liquid/liquid interface was used to compare the situation with that in an emulsion.

From kinetic measurements of the coadsorption we obtained the time-dependent dynamic interfacial tension γ of the mixed layer. The change in the shape and size of the pendent drop with the adsorption time has been observed both through the use of the pure β -lactoglobulin as well as the mixture with phospholipid. After a certain time the drop began to shrink, and a "skinlike" film was formed at the concave curved part of its surface (Figure 1). The detailed

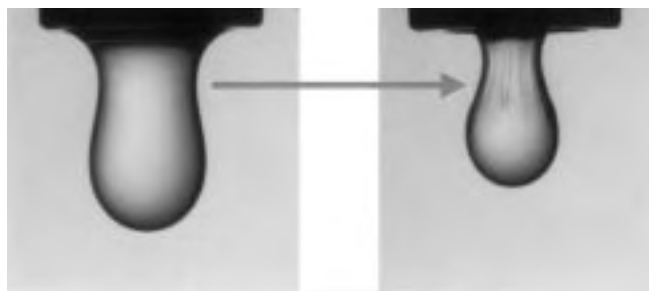


Figure 1. Critical change of the drop surface covered by a monomolecular adsorption layer or by a multilayer film.

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characteristics of drop size and the time to the onset of shrinking (Table 1) depend upon the bulk concentration. At a higher protein concentration, the initial drop size must be reduced to avoid its collapse due to the faster adsorption. The

Table 1. Drop size (V_i initial volume) and characteristic adsorption times of pure β -lactoglobulin at different concentrations. t_1 : time to the onset of shrinking during adsorption; t_2 : time required for the formation of the folded structure at the chloroform/water interface.

$c_{\beta\text{-lactoglobulin}}$ [mg L ⁻¹]	V_i [μ L]	t_1 [s]	t_2 [s]
0.6	15	5380	5670
1.2	15	3500	4300
1.8	13	2720	3150
2.4	12	2090	2600
3.0	12	1920	2430
3.6	12	1890	2270

shrinking began after 1890 s for the highest protein concentration of $c_{\beta\text{-lactoglobulin}} = 3.6 \text{ mg L}^{-1}$, which is nearly three times faster than that for the lowest protein concentration. As a control experiment the system with a β -lactoglobulin concentration of 1.2 mg L^{-1} was selected for further studies of the coadsorption of the mixed phospholipid/protein system. The drop covered by pure protein started to shrink after 3500 s (Figure 2a and b), and had formed a skinlike surface after

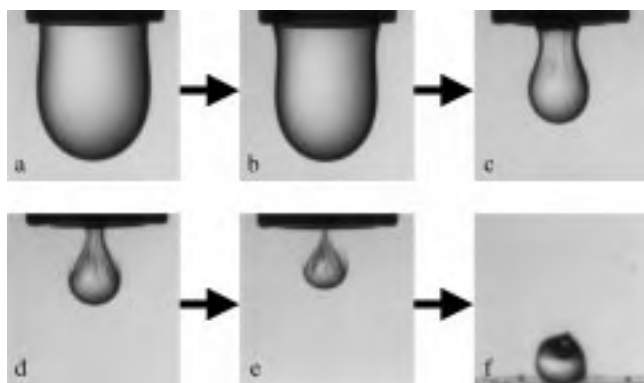


Figure 2. Images of drops covered by β -lactoglobulin or the mixed lipid/ β -lactoglobulin at the chloroform/water interface after different adsorption times. a) A freshly produced β -lactoglobulin drop ($c_{\beta\text{-lactoglobulin}} = 1.2 \text{ mg L}^{-1}$). b) After 3500 s the drop was covered by an adsorption layer of pure protein and started to shrink. c) A skinlike folded drop surface was formed after an adsorption time of 4300 s. d) On addition of DPPC ($c_{\text{DPPC}} = 1 \times 10^{-6} \text{ M}$), the folded drop surface formed already after 3000 s. e) After 4300 s the compressed drop collapsed at the edge close to the tip of the capillary. f) The dropped drop laid on the bottom of the cuvette like a ball.

4300 s (Figure 2c). This process was accelerated by the addition of DPPC to the chloroform solution ($c_{\text{DPPC}} = 1 \times 10^{-6} \text{ M}$) such that the folded surface had already formed after 3000 s. After 4300 s the compressed drop collapsed at the edge close to the tip of capillary (Figure 2d and 2e), and finally dropped to the bottom of the cuvette filled with protein buffer solution (Figure 2f).

On the basis of atomic force microscopy (AFM) measurements, we consider the formation of the skinlike folded surface (Figure 2c–e) as the formation of a multilayer along

the curved surface. For these measurements, we transferred the skinlike folded drop (Figure 2f) to a substrate of mica at the bottom of the cuvette and removed the aqueous solvent by using a Hamilton pump and the organic solvent by evaporation. The remaining film was then examined by surface force microscopy on the top surface and the edge of the skinlike folded drop on mica (Figure 3 and 4).

Figure 3 shows the force microscopy profile of a drop after drying, which was covered with a layer from adsorbed DPPC and β -lactoglobulin and had been transferred onto the mica before the folded surface formed (Figure 2b). The surface morphology clearly reflects that a monolayer is formed. The maximum peak height is 1.7 nm and the diameter regions of aggregated molecules (bright areas) is 35 nm, suggesting that the dried protein was surrounded by phospholipids. The pure phospholipid monolayer has been previously determined to be 2 nm.^[4] Therefore we estimate that the total thickness of the film is in the range of 4–5 nm.

Figure 4C displays images of the scanned top surface of the dried drop (after formation of the fold) on mica. The maximum height of the peak is 1.8 nm and the width of the peak base is 35 nm, respectively. A comparison with Figure 3A shows that here more protein is embedded in the phospholipid layers, indicating that a larger proportion of the protein is adsorbed at the interface and has mixed with the phospholipid. We believe that the two components interact with each other at the interface and stabilize the coadsorbed film. Otherwise gaps would be created by the aggregated protein units, which would have been observable in the three-dimensional (3D) image in Figure 4C. Recent experimental work shows that the β -lactoglobulin is capable of penetrating phospholipid layers as a result of hydrophobic interactions.^[5]

Furthermore, we have studied the fold structure at the edge to the mica substrate through stepwise measurements with the AFM tip. These revealed a thickness of 2.5 μm for the folded film, which indicates the presence of several superimposed layers (Figure 4A); however, each layer is not identical. It is important to realize that one fold layer shown in the image does not represent a single monolayer since the transfer to the mica and the drying of drop could cause an inhomogeneous fold at the edge. Thus if we assume that one DPPC/ β -lactoglobulin layer is 5 nm thick, the overall thickness of 2.5 μm represents a total of 500 layers. Therefore we deduce that the skinlike folding at the neck of the drop is the result of the formation of multilayers.

From previous experiments we have learned that the adsorption of pure DPPC at the same interface can lead to a change in the drop shape with an increasing bulk concentration.^[6] However, a skinlike folded surface has never been observed even

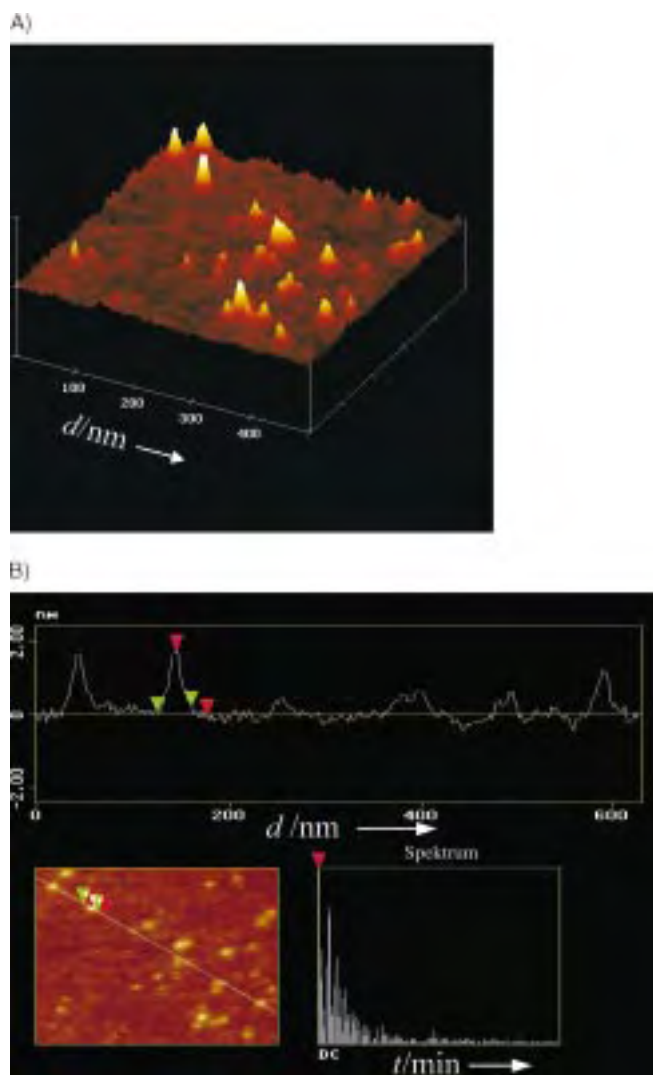


Figure 3. 3D AFM image (A) and height profile (B) of the complex DPPC/ β -lactoglobulin film of an unfolded drop surface transferred onto mica. The transfer onto mica and the drying occurred after an adsorption time of around 3000 s.

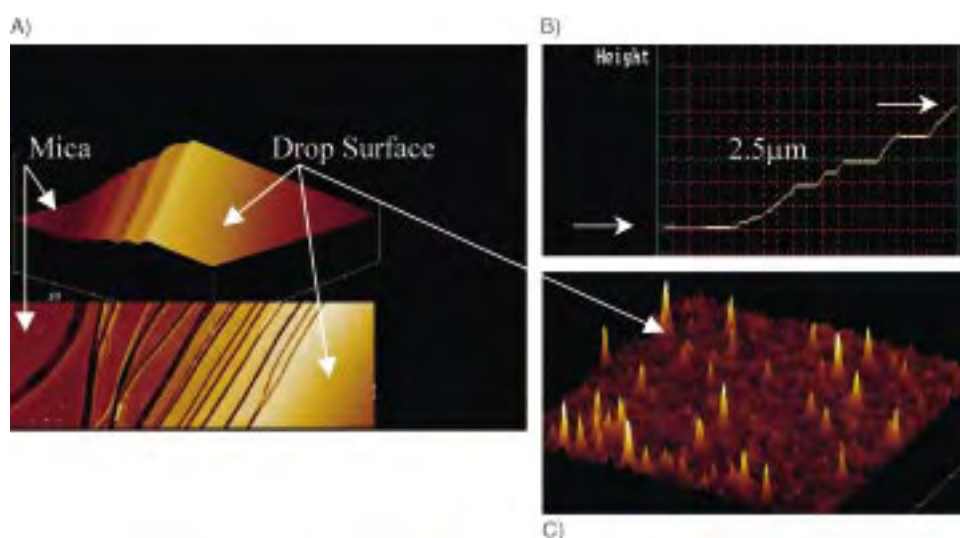


Figure 4. 3D AFM images (A, C) and height profile (B) of the complex DPPC/ β -lactoglobulin film of a folded, skinlike drop surface transferred onto mica. The transfer onto mica and the drying occurred after the collapse of the drop.

for very high bulk concentration (above the critical micelle concentration (CMC)), at which a densely packed adsorption film covers the drop.

Detailed information on the properties of the films are essential for a better understanding of the results. Thus we performed experiments with different headgroups on the lipid and for different pH values of the aqueous phase. *L*- α -dipalmitoylphosphatidylethanolamine (DPPE) has the same chain length as DPPC, but a different headgroup (NH_3^+ instead of NMe_3^+). Under the same conditions, the adsorption of β -lactoglobulin in the presence of DPPE is faster than that in the presence of DPPC, as shown in the kinetics curves in Figure 5 A. Accordingly, the time to the onset of the shrinking

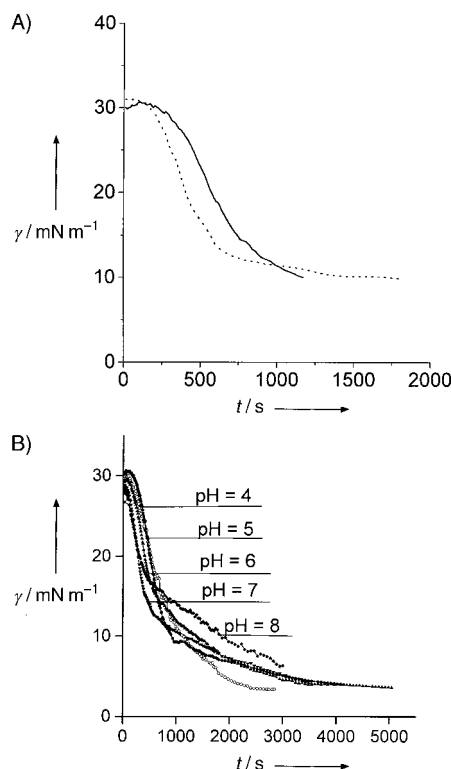


Figure 5. A) Kinetic curves (γ = interfacial tension) of the coadsorption of DPPC (solid line) and DPPE (dotted line) with β -lactoglobulin at the chloroform/water interface at room temperature ($c_{\beta\text{-lactoglobulin}} = 1.2 \text{ mg L}^{-1}$; $c_{\text{lipid}} = 1 \times 10^{-6} \text{ M}$); B) influence of the pH value on the kinetics of the coadsorption of the mixture of DPPC and β -lactoglobulin ($c_{\beta\text{-lactoglobulin}} = 1.2 \text{ mg L}^{-1}$, $c_{\text{DPPC}} = 1 \times 10^{-6} \text{ M}$) at room temperature.

of the drop is 200 s shorter with DPPE than with DPPC. The time for the formation of a skinlike folded surface is also shorter. As expected, the coadsorption kinetics of mixed lipid/protein influenced the rate of the formation of the fold on the surface of the drop and thus the formation of the multilayer.

DPPC is a zwitterionic lipid.^[1, 7] Changes in the pH value of the aqueous phase can influence the charged state of β -lactoglobulin. The isoelectric point of β -lactoglobulin lies at pH 5.2.^[1] Thus between pH 4 and 6 we expect no noticeable influence on the coadsorption behavior. In fact, the kinetic curves in Figure 5 B show the predicted results. At pH values between 7 and 8 both the lipid and β -lactoglobulin carry a negative net charge, and the adsorption rates are similar.

Figure 5 B reveals that the adsorption at pH 7 or 8 is a little faster than at pH 4–6. This effect, however, is not particularly pronounced. This means that the coadsorption is predominantly controlled by the kinetics rather than by electrostatic interactions between the two compounds.

All the adsorption curves finally reach the same plateau, that is the adsorption achieves an equilibrium state. As expected, the pH value has only a very small influence on the rate of adsorption of the DPPC/ β -lactoglobulin mixture, and also the shrinking time of the drop and the time for the formation of the skinlike folded drop surface structure are influenced little by the pH value.

To summarize, a complex film can be constructed at a curved surface by the coadsorption of two components from different subphases. A pure β -lactoglobulin as well as the mixture of DPPC/ β -lactoglobulin can form a skinlike folded film on a drop surface at the chloroform/water interface. The addition of DPPC accelerates the formation of the folded structure at the drop surface by coadsorption with β -lactoglobulin. The AFM analysis provided information on the morphology of the complex film and confirmed the formation of multilayer structures at the liquid/liquid interface.

The design of such complex films can be extended to the gas/water interface and to other two-component systems comprising a water-insoluble amphiphile and water-soluble surfactant. The ability of such systems to form multilayers facilitated the construction of a capsule with a polymer shell by the adsorption of the polyelectrolytes on colloidal templates,^[8] which could be relevant for cosmetic and pharmaceutical applications.

In further work we will focus on the quantitative control of the composition and the structure of the mixed film as well as on the driving force which leads to formation of multilayers on a curved surface. With a smaller capillary with a diameter of about 1 μm it should be possible to form a bubble film.

Experimental Section

L- α -Dipalmitoylphosphatidylcholine (DPPC), *L*- α -dipalmitoylphosphatidylethanolamine (DPPE), and β -lactoglobulin (99% + purity) as well as chloroform (99% purity) were purchased from Sigma and used without further purification. The chloroform was saturated with Millipore water. The protein was dissolved in a 10 mM phosphate buffer solution. All experiments were performed at room temperature.

To measure the adsorption of the pure protein a chloroform drop of sufficient size was generated at the tip of a brass capillary, which was immersed in a solution of the protein in phosphate buffer.

For the determination of the coadsorption of lipid and protein, a few drops of a solution of the lipid in chloroform were initially allowed to drop to the bottom of a cuvette filled with aqueous protein solution, to form a saturated environment, and then a new drop was created. Lipid and protein molecules adsorb on the inside and outside of the chloroform/water interface of the pendent drop, respectively, and thus form a film. The development of the shape of the drop as a function of time was recorded with a CCD camera. Taking into consideration the adsorption time of the two components the interfacial tension γ was determined from the shape and size of the drop. The capture and analysis of the images of the pendent drop was carried out as described in reference [2]. The formation time and lifetime of the drop were recorded precisely by computer.

For the AFM measurements, a cleaned mica plate was carefully placed at the bottom of the cuvette. The cuvette was mechanically raised so that the

mica plate touched the drop before the folding of the surface was established (Figure 2b). The aqueous solution in the cuvette was removed by using a Hamilton pump and the solvent inside was evaporated. The resulting film was studied by surface force microscopy. A similar process was used for the collapsed drop (Figure 2f).

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Chiral Molecular Recognition on Formation of a Metalloanthocyanin: A Supramolecular Metal Complex Pigment from Blue Flowers of *Salvia patens***

Tadao Kondo,* Kin-ichi Oyama, and Kumi Yoshida

Most blue flower color is the result of a metalloanthocyanin,^[1,2] a stoichiometric self-assembled supramolecular pigment consisting of six molecules of an anthocyanin, six molecules of a flavone, and two metal atoms.^[3,4] We have isolated various metalloanthocyanins from the petals of blue flowers and elucidated their structures. We have clarified the mechanisms of the development of blue color by chemical reconstruction of some supramolecules and structural analysis

by NMR spectroscopy and X-ray crystallography.^[1,3] Very fine and strict molecular recognition,^[5] including chiral molecular recognition, occurs during reconstruction. The aromatic chromophores in commelinin and protocyanin stack in a chiral manner, with anticlockwise self-association between two molecules of the anthocyanin or two molecules of the flavone, and clockwise stacking of anthocyanidin and flavone nuclei (co-pigmentation).^[3] These phenomena must arise from the chirality of the sugars attached to the anthocyanidin and flavone units, although, no evidence has hitherto been provided in support of this conclusion.

Herein we describe the chiral molecular recognition on formation of the metalloanthocyanin protodelphin (**1**).^[6] Elucidation of the gross structure of **1**, a genuine pigment from blue petals of *Salvia patens* (Figure 1), demonstrated



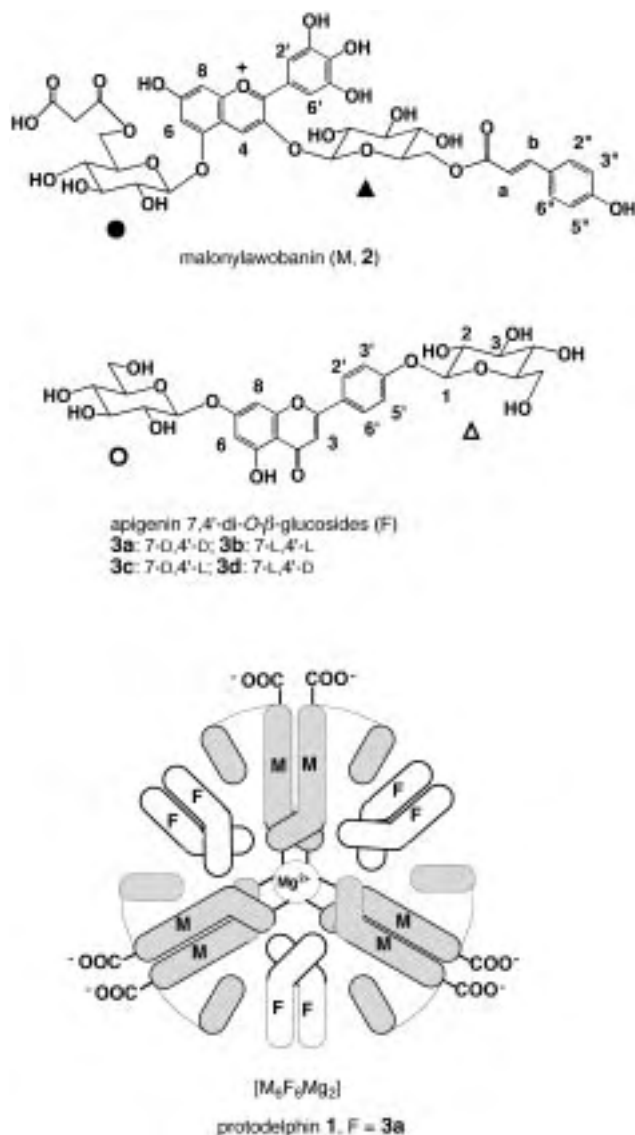
Figure 1. *Salvia patens*.

that it consists of the anthocyanin malonylawobanin (**2**),^[7] the flavone apigenin 7,4'-di-*O*- β -D-glucoside (**3a**),^[6,8] and Mg^{2+} ions (Scheme 1). General and effective synthetic procedures for anthocyanins and/or flavones containing the optically antipodal glycosides are necessary for chiral recognition studies. We have developed a reliable glycosylation method for less-reactive phenols in flavonoids utilizing a new Lewis acid/base promoted glycosylation^[9] with the peracetylglucosyl fluoride (**4**),^[10] and succeeded in preparing natural apigenin 7,4'-di-*O*- β -glucoside **3a** and unnatural derivatives (partly) substituted with L-glucose (**3b–d**). Employment of these synthetic apigenin derivatives and natural **2** in the presence of Mg^{2+} ions allowed an examination of the chiral molecular recognition that occurs during formation of the blue complex pigment.

For the structural determination,^[11] **1** was synthesized from the components according to our reconstruction method.^[3] Compounds **2** and **3a** and Mg^{2+} ions were mixed in a weakly alkaline solution, then the mixture was purified by gel-permeation chromatography/liquid chromatography (GPC-LC)^[12] to give pure protodelphin (**1**) in 61 % yield. The UV/Vis spectra of the product were completely identical with those of the naturally occurring form^[6] (Figure 2). Electrospray ionization mass spectrometry (ESI-MS)^[13] of **1** gave a multiply charged molecular ion at m/z : 1751.8 ($[M - 5H]^{5-}$) corresponding to the constitution $C_{396}H_{408}O_{222}Mg_2$ (average molecular weight: 8767.95, calcd 1751.37 $[M - 5H]^{5-}$). The

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Scheme 1. The structure of components (top and middle) and the entire (bottom) protodelphin. M (**2**) as a bidentate ligand is coordinated to Mg^{2+} ions, and F (**3a**) is intercalated.

CD spectrum (Figure 2) showed a strong negative exciton-type Cotton effect around 620 nm, which indicates that the anthocyanidin nuclei must be closely stacked in an anticlockwise manner, and the ^1H NMR spectrum showed simple signals attributable to one anthocyanin and one flavone residue. Analysis of long-range NOEs between protons of **2** and those of **3a** suggested a cross-parallel arrangement of nuclei. These data indicate that the arrangement of the components in the gross structure of **1** is very similar to that of commelinin. Thus, protodelphin is a stoichiometric supramolecular metal complex pigment, that is, a metalloanthocyanin, similar to commelinin and protocyanin (Scheme 1).

Although glycosylflavones are widely distributed in plants and have attracted attention because of their important biological and medical aspects, only a few syntheses of poly- O -glycosylflavones with satisfactory yield have, surprisingly, been reported. The nucleophilicity of the 4'-hydroxy group on the B-ring of the flavone nucleus is very poor, therefore, there are very few examples of direct 4'- O -glycosylation.^[14]

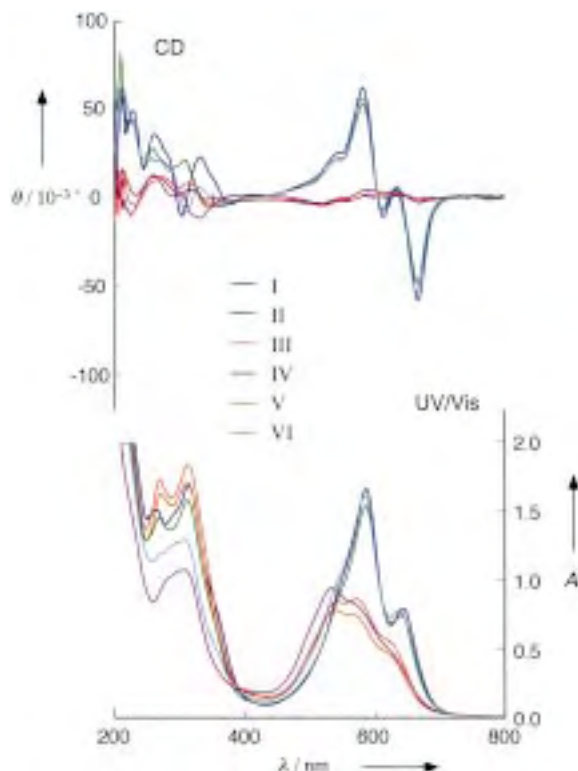
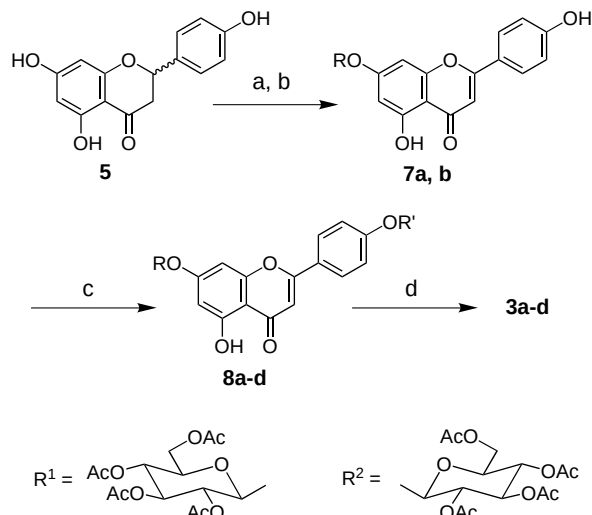


Figure 2. UV/Vis and CD spectra of reconstructed mixtures of **2** (5×10^{-4} M) and **3**, **9**, or **10a** (1 equiv) in the presence of Mg^{2+} ions (5 equiv) in phosphate buffer (pH 6.0). I = **2** + **3a** + Mg^{2+} , II = **2** + **3b** + Mg^{2+} , III = **2** + **3c** + Mg^{2+} , IV = **2** + **3d** + Mg^{2+} , V = **2** + **9** + Mg^{2+} , VI = **2** + **10a** + Mg^{2+} .

We achieved the first synthesis of apigenin 7,4'-di- O - β -D-glucoside (**3a**) by direct glycosylation of the flavone nucleus (Scheme 2). Condensation of naringenin (**5**) with peracetyl-D-glucosyl bromide (**6a**) and consequent oxidization with DDQ



Scheme 2. Synthesis of apigenin 7,4'-di- O - β -D-glucosides **3**: a) peracetylglucosyl bromide (**6a** or **6b**), Ag_2CO_3 , quinoline; b) DDQ, 1,4-dioxane, **7a**: $R = R^1$ (66 %), **7b**: $R = R^2$ (66 %); c) peracetylglucosyl fluoride (**4a** or **4b**), $BF_3 \cdot Et_2O$, DTBMP/TMG (4/1), $CH_2Cl_2/PhCl$ (1/6), **8a**: $R = R' = R^1$ (70 %), **8b**: $R = R' = R^2$ (72 %), **8c**: $R = R^1$, $R' = R^2$ (66 %), **8d**: $R = R^2$, $R' = R^1$ (68 %); d) 1. NaOMe, MeOH/ $CHCl_3$ (2/1); 2. Dowex 50W-8X (H^+), **3a** (92 %), **3b** (88 %), **3c** (92 %), **3d** (94 %). **4a**, **6a**: D-glucosyl; **4b**, **6b**: L-glucosyl. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine; TMG = 1,1,3,3-tetramethylguanidine.

gave the apigenin 7-*O*-peracetyl- β -D-glucoside (**7a**). Treatment of **7a** with peracetyl-D-glucosyl fluoride (**4a**) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$, DTBMP, and TMG afforded apigenin 7,4'-*O*-di- β -D-glucoside as an acetate^[14b] (**8a**) in 70% yield, which was deprotected to yield **3a**. A combination of DTBMP and TMG was essential for the glycosylation of the 4'-OH group of **7a**. By using the same procedure we could prepare a series of unnatural apigenin 7,4'-di-*O*- β -glucosides (**3b–d**) derived from L-glucose: the 7,4'-di-L-glucoside **3b**, 7-D-glucoside-4'-L-glucoside **3c**, and 7-L-glucoside-4'-D-glucoside **3d**.

To clarify the role of the flavone part in the chiral recognition on formation of the metalloanthocyanin, we mixed **2** with **3b–d** in the presence of Mg^{2+} ions. Among the three unnatural apigenin diglucosides used, only **3d** gave a blue solution (Figure 3, IV); **3b** and **3c** gave purple solutions (II and III, respectively). Solution IV showed almost the same UV/Vis and CD spectra as protodelphin (Figure 2), which indicates that a protodelphin-like metalloanthocyanin was produced from **3d**. The stability of the colors of those mixtures was recorded and the results are shown in Figure 3. The color of **1** in a neutral aqueous solution (I) was very stable, while the blue color of IV was less so. The purple color of II and III rapidly faded. To reveal the role of the glucosides at the 7- and 4'-OH groups of apigenin, we prepared apigenin

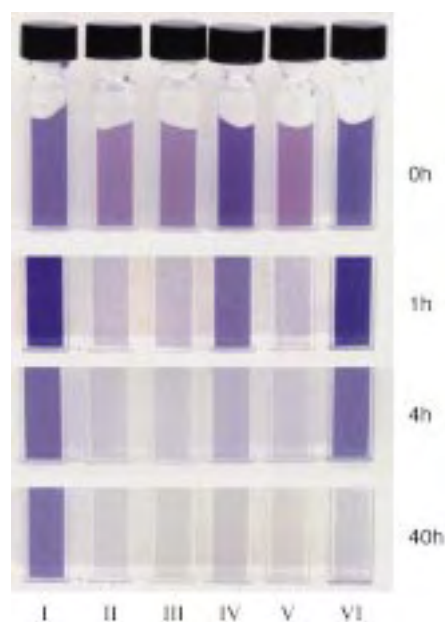


Figure 3. Color stabilities of mixtures of **2** (5×10^{-4} M) and **3**, **9**, or **10a** (1 equiv) in the presence of Mg^{2+} ions (5 equiv) in phosphate buffer (pH 6.0). I = **2** + **3a** + Mg^{2+} , II = **2** + **3b** + Mg^{2+} , III = **2** + **3c** + Mg^{2+} , IV = **2** + **3d** + Mg^{2+} , V = **2** + **9** + Mg^{2+} , VI = **2** + **10a** + Mg^{2+} .

7-*O*- β -D-glucoside^[15] (**9**) and 4'-*O*- β -D-glucoside^[16] (**10a**), respectively, and examined whether a protodelphin-like supramolecule was formed. Compound **10a** gave the blue pigment with **2** and Mg^{2+} ions, but **9** did not (Figure 2, 3). Surprisingly, the blue color of VI, constructed from **10a**, was more stable than that of IV produced from **3d**. Furthermore, we checked its enantiomer, apigenin 4'-*O*- β -L-glucoside (**10b**), for complex formation but no metalloanthocyanin was generated. These phenomena indicate that the D-glucosyl

residue at the 4'-OH position is indispensable for formation of a metal complex pigment. The D-glucose residue at the 7-OH position could stabilize the molecular association, while an L-glucose would destabilize the complex by steric hindrance.

To estimate the enantioselectivity of the molecular recognition on formation of the supramolecule, we attempted a reconstruction experiment from **2** and a 1:1 mixture of **3a** and **3b** with Mg^{2+} ions. The blue mixture was purified by GPC-LC, and a blue-black amorphous mass was obtained in 85% yield. The ratio of **3a** to **3b** in the supramolecule was analyzed by HPLC on a chiral stationary phase.^[17] No peak corresponding to **3b** was observed in the chromatogram, thus the ratio of **3b** to **3a** is less than 2:98.^[18] This result indicated that L,L-diglucoside **3b** was completely excluded from the metal complex. The natural anthocyanin molecule chose only the D-series of glycosylflavones as partners to form metalloanthocyanin.

The high enantioselectivity observed during formation of the supramolecule could be caused by the chiral stacking arrangement of components in **1** as a consequence of the presence of the sugar moiety. Three flavone molecules^[19] in **1** associate to form a *M* (minus) helical structure, similar to a propeller with three blades. They are bound at the pivot point by a strong hydrogen-bonding network among the hydroxyl groups at C-2 and C-3 of the 4'-*O*- β -D-glucopyranosides (Figure 4). The two sets of *M*-helical flavone associates fit closely into the vacant space formed from the metal complex of six molecules of **2** and two Mg^{2+} ions. Replacement of D- by L-glucose at the 4'-OH position of apigenin could invert the helicity to obtain the *P* (plus) form, with the consequence that the associates of the flavones **3b**, **3c**, and **10b** do not fit into the vacant space. Thus, the *M* helicity formed by the three molecules containing the D-glucosyl residue at the 4'-OH site plays a key role in the formation of metalloanthocyanin.

In conclusion, malonylawobanin (**2**) chooses only the D-chirality of the 4'-*O*-glucosyl residue in apigenin 7,4'-diglucoside to form the stoichiometric supramolecular metal complex pigment protodelphin. This restricted chiral and structural recognition controls the entire self-assembly of the metalloanthocyanin and is responsible for the beautiful blue color of the flowers.

Experimental Section

Reconstruction of protodelphin (**1**): *Caution*: the reaction requires concentrations of at least 10^{-2} – 10^{-3} M. A solution of **3a** (20 mg) in water (1 mL) and 0.5 M $\text{Mg}(\text{OAc})_2$ (0.2 mL) was added under stirring at RT to a solution of **2** (34 mg, 35 μmol) in water (0.6 mL) which was neutralized with 1.3% aqueous ammonia. The resulting blue solution was separated by GPC-LC (Cellulofine GC-15-m) to give **1** as a blue-black mass (34 mg, 61%). ¹H NMR (600 MHz, D_2O ; for $\bullet$, $\blacktriangle$, $\circ$, and $\triangle$ see Scheme 1): δ = 4.53 (brd, J = 7.5 Hz, 1H; $\bullet$ -1), 4.77 (brs, 1H; M-8), 4.87 (brd, J = 7.5 Hz, 1H; $\blacktriangle$ -1), 4.94 (brd, J = 7.5 Hz, 1H; $\circ$ -1), 5.13 (brd, J = 7.5 Hz, 1H; $\triangle$ -1), 5.31 (brs, 1H; F-8), 5.52 (brs, 1H; F-3), 5.62 (brs, 1H; M-6), 5.82 (d, J = 16 Hz, 1H; M-a), 5.98 (brs, 1H; F-6), 6.44 (3H; M-3'', 5'', F-2'), 6.62 (brd, 2H; F-2', 3'), 6.73 (1H; M-4), 6.35 (d, J = 9 Hz, 2H; M-2'', 6''), 6.75 (d, J = 16 Hz, 1H; M-b), 5.62 (s, 1H; F-3), 7.46 (brs, 2H; F-5', 6'), 7.79 (brs, 1H; M-6'), 8.10 (brs, 1H; M-2'); MS (ESI): m/z : 1751.8 [M – 5H]⁵⁻.

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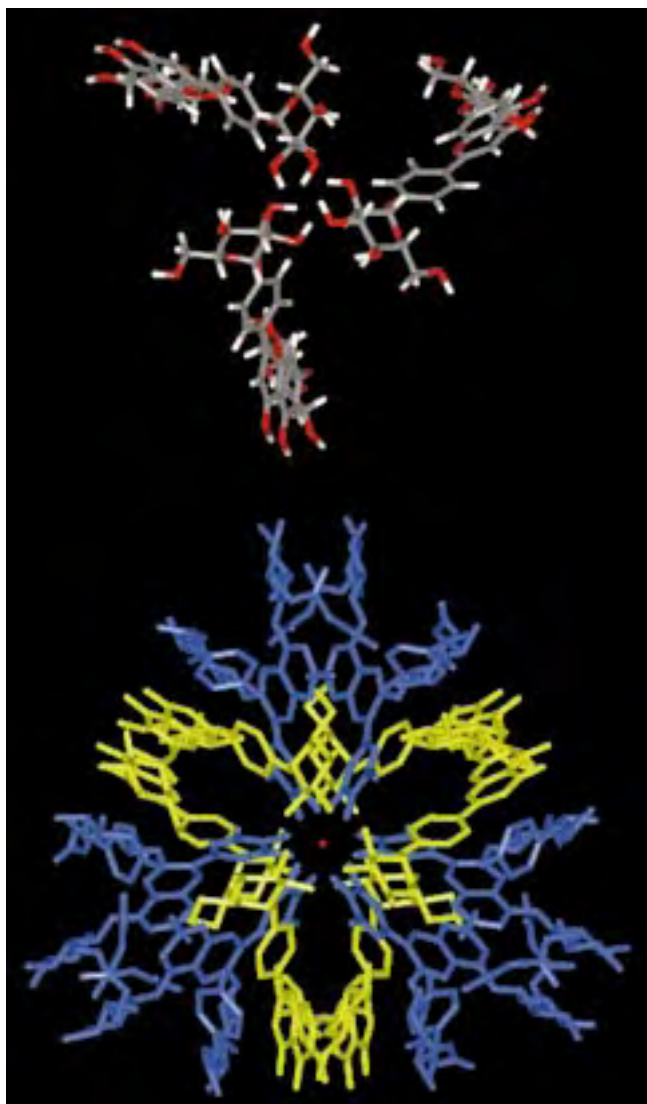


Figure 4. The optimized *M*-helical conformer of three **3a** molecules, similar to a propeller with three blades (top), and the gross structure of **1** (bottom). One set of three F molecules is located at the upper side of the pigment and one at the lower side. The F molecules are intercalated in a face-to-face manner. Mg^{2+} ions exist at both the upper and lower part of the superstructure. The hydrogen atoms are omitted in **1** for clarity. Color scheme: anthocyanin **2**: blue, flavone **3a**: yellow, and Mg^{2+} : red.

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- [16] Apigenin 4'-*O*- β -D- and -L-glucoside (**10a,b**) were prepared according to our procedure. Naringenin (**5**) was selectively silylated at the 7-OH position with *tert*-butyldimethylsilyl chloride/imidazole in DMF. The resulting 7-*O*-silylnaringenin was oxidized, glycosylated with peracetyl-D- or L-glucosyl fluoride, and deprotected with tetrabutylammonium fluoride (TBAF) and MeONa/MeOH to provide **10a,b**.
- [17] Aqueous trifluoroacetic acid (TFA) was added to the produced pigment, then the solution was analyzed by HPLC using a CHIRALCEL OD-R column (DAICEL CHEMICAL) eluted with TFA/ $\text{CH}_3\text{CN}/\text{water}$ 0.3/13/86.7 at RT.
- [18] A mixture of **3a** and **3b** (ratio 98:2) gave two peaks completely separated in HPLC.
- [19] The starting structure of **1** was built by changing the flavocommelin molecule to **3a** on the basis of the crystallographic structure of commelinin.^[3] The local optimization of this structure was performed by QUANTA-97-CHARMM (Ver. 23.2) software.

Synthesis of an Array Comprising 837 Variants of the hYAP WW Protein Domain**

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The elucidation of structure–function relationships of proteins contributes to a better understanding of how they work and also provides clues for the synthesis of agonists and antagonists. Today, variants of the investigated protein required for structure–function analyses are produced almost

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exclusively using recombinant gene technology. The following work sets out to examine whether the SPOT method^[1] can be used for the highly parallel synthesis of proteins required for structure–function analyses. The hYAP WW protein domain was chosen as a model due to its short length of about 40 amino acids.^[2–7] In addition to being one of the smallest protein modules known this domain is a well-investigated model for studying β -sheet motifs.^[4, 6, 8, 9] WW domains have been shown to be of importance in numerous diseases such as Alzheimer's, Chorea Huntington, Liddle's Syndrome, and muscular dystrophy.^[10] WW domains bind to short segments of proline-rich sequences to carry out their function.^[3, 11] The hYAP WW domain binds to the peptide core motif PPXY (X = L-amino acid).^[5, 12]

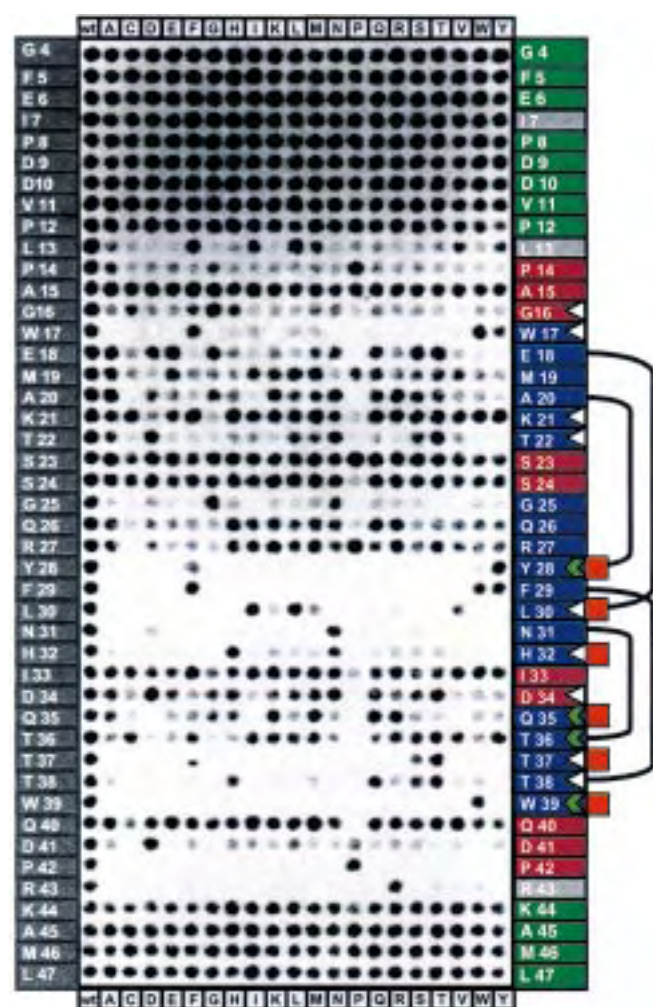


Figure 1. Interaction of the peroxidase-labeled peptide EYPPYPPYPPSG with a library of hYAP WW variants. All spots in the left column comprise the wildtype (wt) sequence of the hYAP WW domain. All other spots contain single substitution variants that can be read out as follows: Rows define the sequence position that is substituted; columns define the amino acid that is used as a replacement. The figure shows the complete single substitution analysis of the hYAP WW protein domain. Numbering of sequence positions and colored marks on the right side refer to NMR structure analyses of the hYAP WW domain:^[4, 13] green rectangles (flexible regions), red rectangles (turn regions), blue rectangles (β -sheet regions), white triangles (chemical shift changes upon ligand binding, approx. 0.2 ppm), green triangles (large changes in chemical shift upon ligand binding, >0.5 ppm), orange squares (domain–ligand contacts) and black brackets (intramolecular hydrogen bonds).

We report the synthesis of an array comprising 837 variants of the hYAP WW domain using stepwise peptide SPOT synthesis on a cellulose membrane and investigation of the binding properties of all variants in the array towards the peptide ligand EYPPYPPYPPSG (Figure 1). To verify binding studies carried out with the array several WW variants were produced by standard methods, then purified and characterized by mass spectrometry. Subsequently, their affinities for the peptide ligand were measured by surface plasmon resonance spectroscopy (Table 1). Affinities of the

Table 1. Binding constants (K_D) and folding status of hYAP WW variants in the absence (Δ) and presence (Σ) of ligand.^[a]

WW variant	K_D [μ M]	Δ	Σ
Wt (G4–L47)	2.4	+++	+++
L13F	4.6	++	++
L13W	22.3	0	+++
L13Y	11.9	+	++
W17Y	8.9	0	++
K21Y	2.5	+++	+++
S23P	3.5	++	+++
S24L	1.5	++	+++
R27P	4.3	+++	+++
L30K	48.6	++	++
H32Y	> 100	+++	+++
V11–A45	2.9	0	+++
P12–K44	7.3	0	++
L13–R43	20.3	0	++

[a] Ratio of folded to unfolded domain was compared to the wildtype (wt = 100%): +++ (>66%), ++ (33%–66%), + (5%–33%), 0 (<5%). Variants in the last three rows represent truncations of the wildtype sequence (Gly4 to Leu47). First and last residues of the sequence are specified in these cases.

purified WW variants range from 1 μ M to 100 μ M and correlate well with signals obtained at the corresponding array positions. Moreover, the folding conditions of the WW variants synthesized conventionally were analyzed by using NMR spectroscopy in the presence and absence of ligand (Table 1). All variants are folded in the presence of ligand. In contrast, in the absence of ligand no folding was detected in five cases. Our results are in accordance with those from analyses of variants produced by recombinant gene technology (Table 2).

The array comprises 837 individual WW variants, each of which differs from the wildtype (wt) at one position. Each of the 44 residues of the WW domain was systematically substituted by each of the common 19 L-amino acids (Figure 1). A comparison of the overall signal pattern with previous structure analyses^[4, 13] reveals correlations between the substitution analysis (Figure 1) and the tertiary structure (Figure 2) of the hYAP WW domain. Insensitivity towards substitutions in the terminal regions of the sequence (positions 4–12 and 44–47) is in accord with a relatively large degree of flexibility of these regions. Furthermore the five positions in the well-ordered central part that are most tolerant towards substitutions (positions 15, 23, 24, 33, 40) are located in turn regions. Positions with a high degree of sensitivity towards substitutions should either have distinct

Table 2. Results from experiments with hYAP WW variants produced by recombinant gene technology.

WW variant	Ligand	Binding	Folding ^[a]	Reference
W17F	GTTPPPYTVG	+	nd	[5]
W17F	EYPPYPPPYPSG	+	+ ^[b]	[6]
Y28F	GTTPPPYTVG	+	nd	[5]
F29Y	GTTPPPYTVG	+	nd	[5]
H32F	GTTPPPYTVG	–	nd	[5]
H32A	GTTPPPYTVG	–	nd	[4]
Q35A	GTTPPPYTVG	+	nd	[5]
W39F	GTTPPPYTVG	–	nd	[5]
W39F	EYPPYPPPYPSG	–	+ ^[c]	[6]
P42A	GTTPPPYTVG	–	nd	[5]

[a] Affinities of WW variants to the peptide ligand were not quantified in most cases. nd = not determined. [b] Folded only in the presence of ligand.

[c] Folded in the presence and absence of ligand.

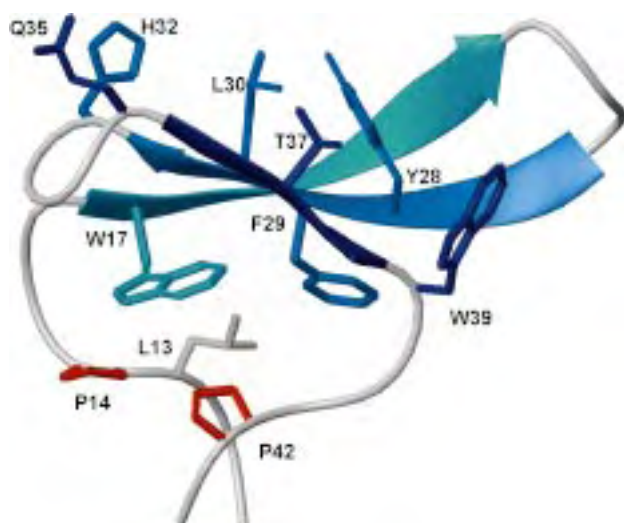


Figure 2. Three-dimensional structure of the hYAP WW domain,^[4] residues V11 to R43 are shown. The triple-stranded β -sheet is colored blue (Figure 1 blue rectangles). Side chains displayed above the surface of the β -sheet form contacts with the ligand. Side chains displayed below the β -sheet form a hydrophobic clamp which is important for stabilizing the overall structure of the domain.

importance in constituting the ligand binding site or have an overall influence on the stable folding of the protein. The three-dimensional structure of the domain–ligand complex facilitates the discrimination between these two cases. Thus the high sensitivity towards substitutions within both C-terminal β -sheet strands (positions 25–32 and 35–39) is feasible since this region constitutes the actual ligand binding site. Also the essential role that Pro42 has for the folding of the protein as the center of a hydrophobic clamp at the back of the β -sheet is reflected by the fact that this position cannot be substituted at all. Clearly observable is the great importance of tryptophans Trp17 and Trp39, accountable for the name of the WW domain family. The structure of the domain ligand complex shows direct contacts between Trp39 and the ligand, whereas Trp17 is located at the back of the β -sheet. While substitutions in position 17 may affect the binding activity of the hYAP WW domain primarily by influencing the stability of the overall domain, substitutions in position 39 should

change the structure of the ligand binding site directly. Restricting the flexibility of the peptide backbone by incorporation of the amino acid proline should only be possible at relatively few positions in a protein structure. Correspondingly, there are only a few positions in the well-ordered region of the domain (positions 13–43) which tolerate the incorporation of proline. In agreement with data from other authors we find that Leu30, which is involved in the formation of the binding pocket, can be substituted by the other aliphatic residues Ile and Val.^[7, 14] Comparison of the sequences of various WW domains revealed that their core motif comprises around 35–40 amino acids.^[15] The substitution analysis and binding studies with three truncated WW variants (Table 1) show that a ligand-binding hYAP WW variant can be limited to the core region V11 to A45 in our case. This variant however is only folded in the presence of ligand (Table 1).

SPOT synthesis^[1] has already proved its value as a tool for the characterization of interactions between peptide ligands and proteins.^[16, 17] In the past however, only libraries of peptide ligands were synthesized on the support surface while the protein was produced by recombinant genetic techniques. The stepwise synthesis of a library of variants of a small protein on the membrane surface, presented in this study, expands this concept for the first time. Earlier work has verified that SPOT synthesis and classical solid-phase methods produce peptides of comparable quality.^[17, 18] Several spots containing hYAP WW wildtype were analyzed to evaluate the quality of the WW domains synthesized on cellulose membranes. The desired product could be identified by mass spectrometry (not shown). However, it could not be excluded that truncated sequences of nonbinding WW variants would bind the ligand and thus might influence the result. Therefore all the single-deletion variants of the hYAP WW wildtype sequence were synthesized by SPOT synthesis and analyzed for peptide ligand binding (not shown). Almost all deletions resulted in loss of binding activity. Only the regions 4–12, 23–24, and 44–47 tolerated missing amino acids. Thus it appears most unlikely that truncated sequences generate false-positive signals. The reproducibility of the synthesis was good, a number of independently synthesized hYAP WW arrays produced the same signal pattern in binding studies. Further indication for a good reproducibility of the synthesis is the similar signal intensity of the 88 wildtype spots in the array (Figure 1).

The work presented here not only reflects the results of previous mutagenesis studies on the hYAP WW domain, but also reveals a number of new insights into the interconnection between structure and function of this protein domain. A systematic analysis of all single substitution variants would have been extremely difficult with recombinant gene technology, since unfolded proteins of this size are generally degraded in situ. Combining the parallel nature of synthesis and subsequent binding studies, provided in our approach, with information regarding the three-dimensional structure results in an efficient tool for the analysis of folding and specificity in small protein domains. Considering recent advancements in the chemical synthesis of proteins^[19] this method for the production of fully synthetic protein arrays should gain increasing significance in the future.

Experimental Section

Synthesis of the WW domain library: The cellulose-bound protein domain library was produced by semi-automatic SPOT synthesis^[1,18] (Abimed, Langenfeld, Germany; software LISA (Jerini AG, Berlin, Germany)) on Whatman 50 cellulose membranes (Whatman, Maidstone, UK), as described in ref. [20].

HPLC-MS analysis of cellulose-bound wildtype hYAP WW domains: Ten spots (approx. 3 nmol peptide per spot) were punched out of the cellulose membrane. The peptides bound to the solid phase through an ester linkage were cleaved off by treatment with NH₃ gas for 16 h. The peptide was then eluted from the membrane with H₂O/trifluoroacetic acid (0.5%) and analyzed by using HPLC-MS. System: Hewlett-Packard series 1100 coupled with a Finnigan LCQ Ion Trap ESI mass spectrometer; column: Vydac C18, 150 × 2.1 mm, 5 μm; flow rate: 0.3 mL min⁻¹; gradient: 5% – 95% B (= acetonitrile) in 17 min. The desired product was identified with a retention time of 10.1 min.

Labeling of the peptide ligand: The peptide ligand CββEYPPYPPYPSPG (β = β-alanine) was linked through the cysteine group to maleimide-activated horseradish peroxidase (Pierce, Rockford, IL) according to the supplier's instructions. Remaining maleimido groups were deactivated with a tenfold excess of sulfanylethanol (1 h, RT), followed by dialysis against TBS buffer (50 mM tris(hydroxymethyl)aminomethane (Tris), 100 mM NaCl, pH 8.0).

Incubation and development of the membrane: Membrane-bound WW domains were incubated overnight in blocking buffer (10% blocking reagent (CRB, Norwich, UK), 1% sucrose in TBS buffer). Subsequently, the labeled peptide ligand (2 μg mL⁻¹) was incubated with the membrane in the same buffer at 4 °C overnight then washed five times with TBS. A chemiluminescent substrate (Pierce, Rockford, IL) and a luminescence detector (Lumi-Imager, Boehringer Mannheim, Mannheim, Germany) were employed for detection.

Synthesis of peptide ligands and soluble WW variants for binding and folding studies: Syntheses were carried out according to standard Fmoc protocols (Fmoc = 9-fluorenylmethoxycarbonyl) with an automated peptide synthesizer (Abimed, Langenfeld, Germany). The products were purified by using HPLC and analyzed by MALDI-TOF mass spectrometry.

Measuring of binding affinities of WW variants to peptide ligands: Measurements were made with a BIAcoreX system in HBS buffer (10 mM 2-[4-(2-hydroxyethyl)-1-piperazin]ethanesulfonic acid (HEPES), pH 7.4, 150 mM NaCl, 3 mM ethylenediamine-N,N,N', N'-tetraacetic acid (EDTA), 0.005% polysorbate-20). The peptide ligand CββEYPPYPPYPSPG was immobilized on a CM5-sensorchip through the cysteine group with the ligand–thiol method, according to supplier's instructions. The amount of immobilized ligand corresponded to a signal increase of 400 resonance units (RU). An equivalent amount of the nonbinding peptide CββEAPPAPPPAPSPG was immobilized in the reference cell using the same procedure. Binding experiments were performed with WW variant concentrations ranging from 200 nM to 125 μM (eight different concentrations were applied for each experiment). Binding experiments were performed at 25 °C with a flow rate of 15 μL min⁻¹. Data were evaluated with the software BIAevaluation 3.0 according to the steady-state procedure.

Determining the folding status of WW variants using NMR spectroscopy: ¹H NMR spectra of WW variants (1 mM) and WW variants in complexes with the peptide ligand KββEYPPYPPYPSPG in a molar proportion of 1:2 were recorded on a 600 MHz DRX Bruker spectrometer. Experiments were carried out in 10 mM aqueous phosphate buffer, pH 6.0, 100 mM NaCl, 0.1 mM dithiothreitol (DTT), 0.1 mM EDTA at 15 °C. To determine the folding status of WW variants the proportion of the surface areas of the folding-dependent indole NH signal of W17 (δ = 10.27) and W39 (δ = 9.96) in the folded respectively unfolded states (both δ = 10.05) were compared.^[6, 9]

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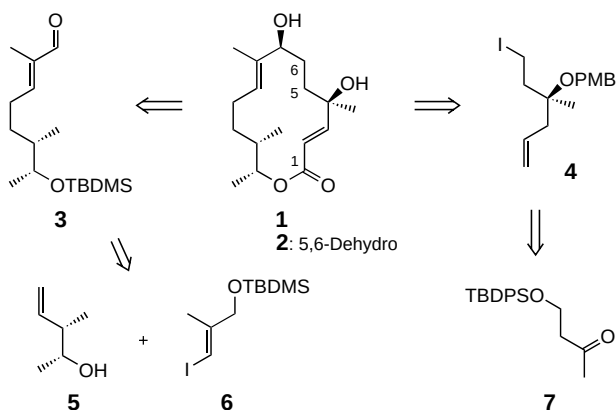
Total Synthesis of the Macrolide Antibiotic 5,6-Dihydrocineromycin B**

Lutz F. Tietze* und Ludwig Völkel

Dedicated to Professor Burchard Franck on the occasion of his 75th birthday

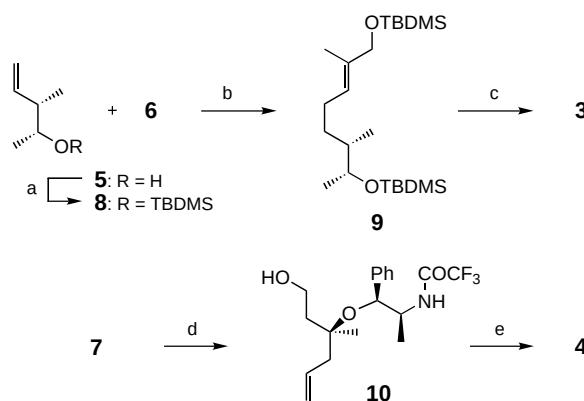
5,6-Dihydrocineromycin B (**1**) belongs to the group of macrolide antibiotics with a 14-membered lactone functionality and has been isolated recently from *Streptomyces* sp. Gö 40/10 together with cineromycin B (**2**) and other metabolites by Zeeck et al.^[1] The group of cineromycins and albocyclins—18 compounds are currently known—are particularly important due to their antibiotic activity against staphylococci. To date only one report has appeared in which the syntheses of this class of compounds is described.^[2] Here we outline the first total synthesis of 5,6-dihydrocineromycin B (**1**) as well as that of the 7-*epi* diastereomer **17** and of the corresponding 2,3,5,6-tetrahydro compound **14**.

The retrosynthesis of **1** leads to the chiral building blocks **3** and **4** (Scheme 1). Compound **3** can be obtained from the known homoallyl alcohol **5**^[3] and the vinyl iodide **6**;^[4] the tertiary homoallyl ether **4** is accessed through a facial selective allylation^[5] of the ketone **7**.



Scheme 1. Retrosynthesis of 5,6-dihydrocineromycin B (**1**). TBDMS = *tert*-butyldimethylsilyl, PMB = 4-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl.

The alcohol **5** was converted into the silyl-protected compound **8** and then intermediary by reaction with 9-BBN into the corresponding borane for the cross coupling with **6** (Scheme 2).^[6] In the subsequent reaction with **6**, a small variation of the reaction conditions usually applied for such couplings, led to a considerable increase in the yield and rate



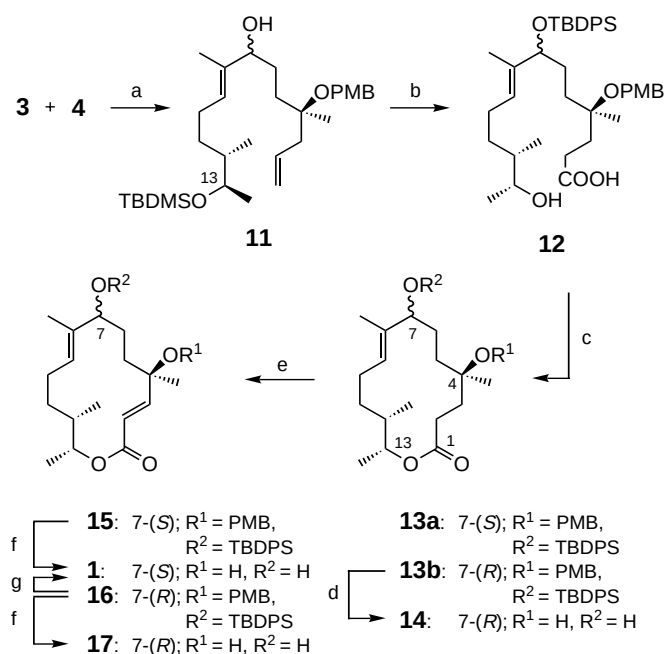
Scheme 2. a) TBDMSCl, imidazole, DMF, DMAP, RT, 100%; b) **8**, 9-BBN, THF, 0 °C → RT, then **6**, DMF, 2.8 equiv H₂O, K₃PO₄, 5 mol % [PdCl₂(dppf)], RT, 85%; c) 1. 40% HF(aq)/pyridine 1:10, RT, 89%; 2. MnO₂, CH₂Cl₂, RT, 96%; d) 1. 2 equiv **7**, 2 equiv allyltrimethylsilane, 1 equiv of the trimethylsilyl ether of *N*-trifluoroacetamidonorpseudoephedrine, 0.2 equiv TfOH, CH₂Cl₂, −78 °C, 17 h; 2. crude product, 40% HF(aq), CH₂Cl₂, RT, crystallization from pentane/*t*BuOMe, 73%, *ds* > 99:1; e) 1. Li, NH₃/THF, −78 °C, then NH₄Cl, 90%; 2. TBDPSCl, DMAP, imidazole, DMF, RT, 99%; 3. PMBO(NH)CCl₃, cat. TfOH, Et₂O, 0 °C; 4. crude product, TBAF·3H₂O, THF, 50 °C, 66%; 5. I₂, imidazole, PPh₃, CH₂Cl₂, RT, 90%. DMAP = 4-dimethylaminopyridine, 9-BBN = 9-borabicyclo[3.3.1]nonane, Tf = trifluoromethanesulfonyl, TBAF = tetrabutylammonium fluoride.

of reaction: The reaction with K₃PO₄ as base and DMF as solvent at 50 °C for 6–24 h under dry conditions in the presence of catalytic amounts of [PdCl₂(dppf)] (dppf = bis-(diphenylphosphanyl)ferrocene) gave **9** with a moderate yield of 18–37%. On the other hand, addition of a small amount of water to the reaction mixture led, after 5 h at 25 °C, to a yield of 85%. The selective cleavage of the primary silyl ether unit in **9** with HF(aq)/pyridine, followed by oxidation with manganese dioxide gave **3** in 85% yield. The building block **4** was generated by converting the ketone **7**, in accordance with our previously described method,^[5] followed by cleavage of the silyl ether, into the diastereomerically pure homoallyl ether **10**. Removal of the auxiliaries from **10**, followed by introduction of a 4-methoxybenzyl group at the tertiary hydroxy group and the replacement of the primary hydroxy group with an iodine substituent gave the desired product with an *ee* value of >99%.

We have also carried out this synthesis sequence with a *tert*-butyldimethylsilyl group at the tertiary hydroxy group; unfortunately on deprotection of the 2,3,5,6-tetrahydro derivative of cineromycin B (**2**) at the end of the synthesis, a complete rearrangement of the 14-membered lactone ring to give a γ -lactone occurred, forcing us to choose another protecting group. For the 1,2-addition to the α,β -unsaturated aldehyde **3**, the iodide **4** was allowed to react with *sec*-butyllithium at −78 °C 10 min (Scheme 3). (With longer reaction times or use of *tert*-butyllithium, deprotonation of the 4-methoxybenzyl group at C-4 and subsequent Wittig rearrangement become more pronounced.^[7]) The addition on **3** gave the allyl alcohol **11** as a 1:1 mixture: attempts to carry out the reaction selectively according to the method developed by Knochel et al.,^[8] failed because the corresponding organozinc compound was inaccessible. Protection of the

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Scheme 3. a) **4**, 1.8 equiv *s*BuLi, Et₂O, -78 °C, 10 min, then **3**, Et₂O, 10 min, then MeOH, 68%; b) 1. TBDPSCl, imidazole, DMAP, DMF, 50 °C, 90%; 2. 9-BBN, THF, 50 °C, then H₂O₂, NaOH, 78%; 3. IBX, THF/DMF 1:1, RT; 4. NaClO₂, NaH₂PO₄, *t*BuOH, 2-methyl-2-butene, H₂O, RT, then crude product, 40% HF(aq)/pyridine 1:1, EtCN, RT, 67%; c) 2,4,6-trichlorobenzoyl chloride, *i*Pr₂NEt, THF, 0 °C, then toluene, DMAP, RT, 86%; d) 1. HF·pyridine/pyridine 1:3, 60 °C, 73%; 2. DDQ, CH₂Cl₂/H₂O 30:1, 0 °C, 5 min, ca. 60%; e) LHMDS, TMSCl, THF, -78 °C, then CH₃CN, MS 3 Å, Pd(OAc)₂, RT, **15**: 38%, **16**: 59%; f) 1. as (d), step 2, 15 min; 2. as (d), step 1, two steps, **1**: 49%, **17**: 50%; g) 1. as (d), step 1, 72%; 2. as (b), step 3, 90%; 3. (*S*)-BINAL-H, see ref. [11], 72%; 4. as (d), step 2, 15 min, 51%. LHMDS = lithium hexamethyldisilazide, TMS = trimethylsilyl.

allyl hydroxy group in **11**, followed by rearrangement of the double bond and selective cleavage of the protecting group of the secondary hydroxy group on C-13 gave the acyclic carbonic acid **12**, from which the lactone **13** was obtained by Yamaguchi lactonization^[9] on reaction with 2,4,6-trichlorobenzoyl chloride. The synthesized diastereomeric macrocycles **13a** and **13b** can be separated easily by column chromatography on silica gel. The diastereomers were assigned by comparison of the data of **1** produced from **13a** with the literature data.^[1a]

The 2,3-double bond was introduced in **13a** and **13b** by using a modified procedure from Saegusa et al.^[10] by conversion into the silyl enol ether followed by oxidation with Pd(OAc)₂. This gave the 7-*epi* derivative **16** and the diastereomer **15** in yields of 59 and 38%, respectively, under identical reaction conditions. The formation of the α -silylated macro-lactone in a competing reaction was responsible for the latter result; remarkably its formation proceeds in a stereochemically uniform manner. The final transformation of **15** into the natural product **1** was achieved by removal of the two protecting groups with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) and with the HF·pyridine complex in pyridine at 60 °C in 46% yield. The 7-*epi* derivative **17** was obtained from **16** in a similar manner. Moreover, the 2,3,5,6-tetrahydro derivative **14** was synthesized from **13b**; however, this

compound is only stable for a short time at room temperature due to its tendency to rearrange to the γ -lactone. The synthetic compound **1** is identical to the natural product.^[1a]

An improvement of the selectivity in the formation of **1** occurs on removal of the silyl protecting group in **16** and oxidation with IBX (*o*-iodoxybenzoic acid; 1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide).^[11] The resulting enone can be reduced in a 6:1 selectivity to the corresponding *S*-configured allyl alcohol on reaction with (*S*)-BINAL-H^[12] and be converted into **1** by oxidative deprotection.

The presented concept for the first total synthesis of 5,6-dihydrocineromycin B (**1**) offers a flexible and convergent access to the cineromycins. The key step hereby is our selective synthesis of enantiomerically pure tertiary alcohols by allylation of ketones.

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A Novel Concept in Combinatorial Chemistry in Solution with the Advantages of Solid-Phase Synthesis: Formation of N-Betaines by Multicomponent Domino Reactions**

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*Dedicated to Professor Ivar Ugi
on the occasion of his 70th birthday*

Combinatorial chemistry is an important method, both in the search for lead structures of pharmacologically active compounds and in their optimization,^[1] and it also finds application in supramolecular chemistry,^[2] in catalyst development,^[3] and in material science.^[4] Within this context combinatorial solid-phase synthesis^[5] has the advantage of simple automation, since reagents can be used in excess, and impurities and by-products can be removed by simple filtration and washing procedures. Frequently, however, the transfer of reactions established in solution to the solid phase is fraught with difficulties; an additional disadvantage is that the synthesis is extended by two steps. Moreover, monitoring the course of the reaction on the solid phase is problematic using normal methods. Therefore, parallel to solid-phase synthesis new combinatorial approaches to synthesis in solution, to reactions on soluble resins,^[6] and in the perfluorinated phase,^[7] as well as separation of by-products by binding to polymers^[8] have been developed.

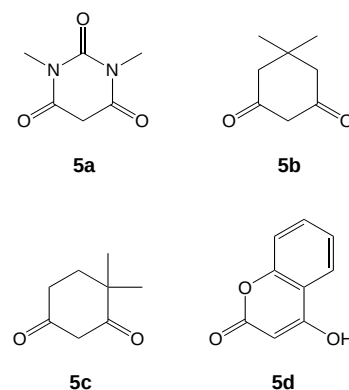
Herein we describe a new, simple concept in combinatorial chemistry which combines the advantages of reactions in solution with those of solid-phase synthesis. The reagents can be used in excess, and the products can be obtained by simple precipitation in purities of up to 99 %. The procedure involves a multicomponent domino Knoevenagel/hetero-Diels–Alder reaction^[9] of a 1,3-dicarbonyl compound with an amino aldehyde and an enol ether, followed by a reductive amination with the formation of a betaine which can be precipitated from the solution in high purity. Organic by-products and excess reagents are separated by simple filtration. By the use of α -, β -, and γ -amino aldehydes libraries of pyrrolidine, piperidine, and azepane derivatives, respectively, may be obtained.

The required amino aldehydes **1–3** are accessible in high yields simply by reaction of a wide spectrum of available natural and nonnatural α -, β -, and γ -amino acids with benzyl chloroformate, followed by esterification, and reduction with diisobutylaluminum hydride (DIBAL-H) in hexane solution (Table 1).^[10] The compounds are stable and storable. *N,N'*-

Table 1. Amino aldehydes used.

Aminoaldehyde	R ¹	R ²	n
1a	H	H	0
1b	H	Me	0
1c	Me	H	0
1d	<i>i</i> Pr	H	0
1e	<i>i</i> Bu	H	0
1f	Bn	H	0
1g	CH ₂ CH ₂ CH ₂		0
2	H	H	1
3	H	H	2

dimethylbarbituric acid (**5a**), the cyclohexan-1,3-diones **5b** and **5c**, and 4-hydroxycoumarin (**5d**) were used as 1,3-dicarbonyl components. The differently substituted benzyl enol ethers **4a–d**^[11] served as dienophiles.



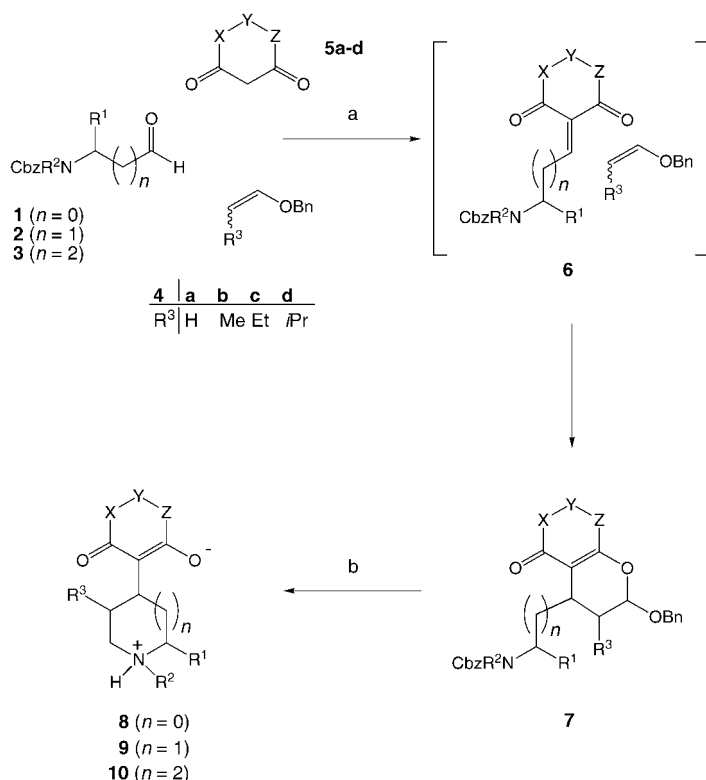
The amino aldehydes **1–3** were treated with the 1,3-dicarbonyl components **5a–d** (1 equiv) and the benzyl enol ethers **4a–d** (4 equiv) in toluene in the presence of catalytic amounts of EDDA and trimethyl orthoformate as dehydrating agent in an ultrasonic bath at 50 °C (Scheme 1). Knoevenagel condensation of the amino aldehyde with the 1,3-dicarbonyl component occurs first with the formation of an electron-deficient, sterically fixed 1-oxo-1,3-butadiene **6** which then reacts with the benzyl enol ether in a Diels–Alder reaction with inverse-electron demand to afford a benzyl-protected acetal **7**. Subsequent hydrogenation with palladium on carbon as catalyst leads to hydrogenolysis of the benzyl acetal and the Cbz protecting group with release of an amine and an aldehyde, which under the reaction conditions lead to the desired highly substituted nitrogen heterocycles **8–10** of different ring size in an intramolecular reductive amination (Scheme 2, Table 2); mixtures of diastereoisomers are normally formed in the reaction.

The products thus obtained contain a 1,3-dicarbonyl unit with an C–H-acidic methylene group and an amino group; this leads to the formation of a betaine which is readily soluble in water and methanol, but can be precipitated by the addition of diethyl ether. This represents a new concept in combinatorial chemistry which should find general applicability. The scope of the procedure is considerable; for example, sterically demanding amino aldehydes and benzyl enol ethers could be used. The use of 1,3-dicarbonyl compounds with reduced reactivity did not result in a deterioration of the purity of the

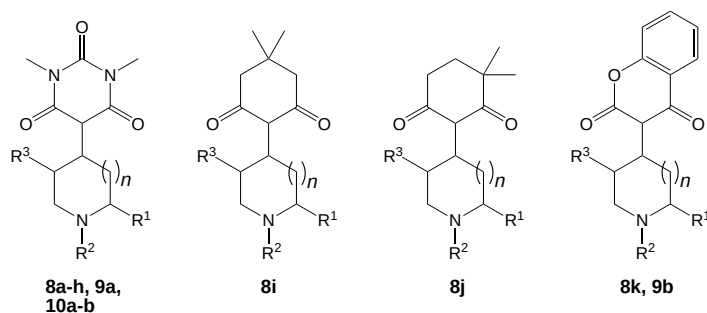
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 1. Domino sequence comprising Knoevenagel, hetero-Diels–Alder reaction, and hydrogenation starting from amino aldehydes, 1,3-dicarbonyl compounds, and enol ethers. a) toluene, EDDA, ultrasound, 50 °C, 15 h; b) Pd/C, H₂, 1 bar, RT, 24 h. EDDA = ethylenediammonium diacetate, Cbz = benzyl-oxycarbonyl, Bn = Benzyl.



Scheme 2. Products from the domino Knoevenagel/hetero-Diels–Alder/hydrogenation sequence.

products, in spite of the required extended reaction times. Only reaction with the disubstituted *N*-Cbz-2-amino-2-methylpropionaldehyde and benzyl-2-methylprop-1-enyl ether did not lead to the desired products, presumably because of steric overload.

Unlike solid-phase combinatorial chemistry the reactions may be monitored at all times by thin-layer chromatography, and where required the intermediates investigated without difficulty by normal spectroscopic methods. Finally, one further advantage is the lack of requirement for the use of expensive resins as well as the development and optimization of suitable coupling and decoupling reactions. The domino sequence of Knoevenagel, hetero-Diels–Alder reaction, and hydrogenation allows rapid access to a number of N-hetero-

Table 2. Products of the domino sequence: pyrrolidine, piperidine, and azepane derivatives **8**, **9**, and **10**, respectively.

Product	R ¹	R ²	R ³	<i>n</i>	Purity [%] ^[a]	Yield [%]
8a	H	H	Et	0	97	53
8b	H	Me	<i>i</i> Pr	0	> 90 ^[b]	47
8c	Me	H	Me	0	97	45
8d	<i>i</i> Pr	H	H	0	95	55
8e	<i>i</i> Bu	H	H	0	99	59
8f	<i>i</i> Bu	H	Et	0	> 95	41
8g	CH ₂ CH ₂ CH ₂	H	0	> 90	51	
8h	Bn	H	H	0	97	65
8i	Me	H	H	0	> 95	71
8j	Me	H	H	0	> 95	59
8k	Me	H	H	0	95	61
9a	H	H	H	1	> 95	60
9b	H	H	H	1	> 95	69
10a	H	H	H	2	98	58
10b	H	H	Me	2	> 95	55

[a] Determined by HPLC unless otherwise indicated. [b] Purity determined by ¹H NMR spectroscopy.

cycles of different ring sizes and substitution patterns with a betaine structure which can be obtained in high purity by precipitation in a process which is also suitable for automation.

Experimental Section

Synthesis of **8h**: **1f** (35.4 mg, 125 μmol), *N,N'*-dimethylbarbituric acid (**5a**) (19.5 mg, 125 μmol) and benzylvinyl ether (**4a**) (134 mg, 1.00 mmol) were allowed to react in toluene (0.5 mL) and trimethyl orthoformate (0.1 mL) with a few crystals of EDDA in an argon atmosphere in a 10-mL pressure flask in an ultrasonic bath for 15 h at 50–60 °C. After removal of the solvent in vacuo, the residue was dissolved in methanol (4 mL) and stirred in a hydrogen atmosphere in the presence of palladium on carbon (10%, 12.5 mg) for 24 h. Subsequently, the catalyst was removed by filtration through a little celite, washed with methanol, and the solvent removed in vacuo. The residue was dissolved in a little methanol and the product was precipitated by the addition of diethyl ether. The white, amorphous precipitate was filtered off and washed with diethyl ether. Compound **8h** was 97% pure as determined by HPLC. Decomposition > 250 °C; ¹H NMR (300 MHz, CD₃OD): δ = 2.05–2.45 (2 m, 2H; 4-H), 2.90–2.95 (m, 2H; PhCH₂), 3.20 (s, 6H; 2 × NCH₃), 3.30–3.55 (m, 3H; 2-H, 5-H), 4.22–4.32 (m, 1H; 3-H), 7.15–7.30 (m, 5H; Ph-H); ¹³C NMR (75 MHz, [D₆]DMSO): δ = 26.17 (2 × NCH₃), 27.21 (C-4), 39.87 (C-3), 35.28, 43.49 (C-1', C-5), 61.83 (C-2), 81.15 (C-5'), 125.5, 128.3, 128.7 (C-3'', C-4'', C-5'', C-6'') 131.0 (C-2''), 152.6 (C-2'), 162.0 (C-4', C-6'); MS (70 eV): *m/z* (%): 315.2 (1) [*M*⁺], 224.1 (100) [*M*⁺ – Bn], 91.0 (10) [C₇H₇⁺]; HR-MS: calcd for C₁₇H₂₁N₃O₃: 315.1582, found: 315.1582.

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Spatially Resolved Detection of Neurotransmitter Secretion from Individual Cells by Means of Scanning Electrochemical Microscopy

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Microelectrochemical methods, especially constant-potential amperometry and fast-scan cyclic voltammetry,^[1] provide possibilities to investigate biological systems with cellular or subcellular spatial resolution determined mainly by the size of the available microelectrodes.^[2] Among the biological phenomena studied so far at single cells or substructures of single cells are individual exocytosis events,^[3] oxygen consumption,^[4] photosynthetic activity,^[5] and ion channel distribu-

tion.^[6] In these experiments, the electrochemical sensor—usually a microdisk electrode with a tip diameter of a few micrometers—has to be positioned in close proximity to the object. The approach of the microelectrode to the biological object is, in general, performed under control of an optical microscope using manual- or piezo-actuated micromanipulators for positioning of the sensor tip. The electrode is slowly moved towards the cell until it slightly touches the cell membrane, which is visualized by its bending. The tip is then retracted for a defined distance allowing, in principal, adjustment of the membrane-to-electrode distance within a range of several hundred nanometers to two micrometers. Although this approach has been successfully used in recent years,^[3] there are significant drawbacks, such as a) possible contamination of the electrode surface due to its contact with the cell membrane, b) insufficient reproducibility of the tip-to-cell distance, which becomes even more difficult using smaller microelectrodes, that are hardly visible in the optical microscope, c) eventual deterioration of the cell at the contact point or mechanical depolarization of the cell, and d) the impossibility to investigate sequentially different spots on the same cell.

After initial investigations of biological samples by means of scanning electrochemical microscopy (SECM),^[7] attempts have been recently undertaken to visualize the metabolism and the redox activity of individual cells.^[8] However, one of the major problems in conventional SECM experiments is the constant *z*-height of the microelectrode, which does not allow differentiation between variations in the tip-to-sample distance and changes of the local electrochemical activity. In order to overcome these limitations, we have introduced a shear-force based constant-distance control into the SECM.^[9] The benefits and limitations had been described in detail recently.^[10] In short, the microelectrode vibrates at its resonance frequency with typical amplitudes of only a few nanometers with use of a piezo-pusher. Simultaneously, a laser beam is focused onto the very end of the vibrating electrode and the resulting Fresnel diffraction pattern is projected onto a split photodiode. Amplitude and phase information about the vibrating tip is obtained by the amplification of the difference signal from the split photodiode with respect to the agitation signal using a lock-in amplifier. With decreasing tip-to-sample distance, increasing shear forces between tip and sample surface lead to a damping of the vibration amplitude and to a phase shift, which can be used to continuously keep a predefined damping value related to a constant distance of about 50–100 nm by means of a software-controlled feedback loop.

Thus, adaptation of the shear-force based constant-distance control of the tip-to-sample gap to biological preparations at the single-cell level should, on the one hand, allow the problems occurring with manual microelectrode positioning to be overcome and, on the other hand, enable detectable variations of chemical species at different sites of a biological preparation.

Using platinum microelectrodes sealed in glass capillaries, which can be easily positioned over hard sample surfaces using the shear-force positioning mode, no satisfying results could be obtained. In preliminary experiments using adher-

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ently growing cultures of living Retzius cells (from the medicinal leech with a typical diameter of about 80 μm) and PC12 cells (a pheochromocytoma tumor cell line with a typical diameter of 12 μm and a height of about 10 μm), the cells were cut into pieces by the vibrating microelectrode or peeled off the surface and locally displaced.

Thus, a successful adaptation of the shear-force based distance-control to soft biological samples is only possible if the force of interaction between the vibrating tip and the biological sample can be minimized. In addition, the shear-force detection has to be optimized with the vibrating microelectrode immersed into liquids and, concomitantly, the overall dimensions of the microelectrode tip have to be kept as small as possible in order to limit the distortions arising from mismatch between tip size and topography of the sample.^[11] In order to evaluate the necessary stiffness, resonance frequency, and vibration amplitude, which allows visualization of the topography of a living cell using the shear-force mode, glass capillaries have been drawn to provide overall tip diameters in the range of 5–50 μm . Glass capillaries with tip dimensions of about 5–15 μm and resonance frequencies in the range 1–5 kHz showed a response to topographical changes while scanning over adherently growing Retzius cells (Figure 1) without any deterioration of the cells.

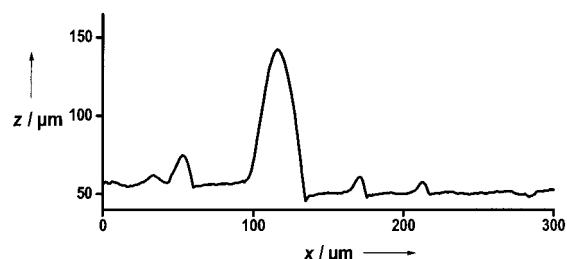


Figure 1. Shear-force based topographical imaging of fragile biological samples: Line scan across a neuron of the medicinal leech (Retzius cell) using a glass capillary with a tip diameter of about 5 μm .

Based on these results, microelectrodes had to be developed showing similar stiffness and vibration characteristics, in order to implement electrochemical detection into shear-force based imaging. Carbon fibers, which exhibit mechanical properties similar to pulled-glass capillaries, have been widely used as microelectrodes in manual approach experiments and several methods have been described to apply a thin insulating layer onto carbon fibers, either using electrochemically deposited polymers (for example polyphenol)^[12] or the pH-induced electrodeposition of a lacquer paint.^[13] In contrast to the self-limiting film growth of polyphenol, the pH-induced electrodeposition of a paint is followed by a heat-curing process to crosslink the initially deposited prepolymer to an insulating film. A disk-shaped electrode surface is exposed by cutting the tip with a scalpel. For the proper adaptation of the stiffness of carbon-fiber microelectrodes, the electrodeposition of an insulating paint has the advantage that the films can be grown to any suitable thickness by varying the deposition voltage and deposition time. In addition, suitable vibration properties of the carbon-fiber electrodes were obtained after

dip coating the fiber in insulating varnish,^[14] which resulted in an increase of the resonance frequency with the number of coating layers. The best results with regard to electrochemical quality and stability of the vibration properties were achieved by combining the electrodeposition and the dip-coating method. Parts of the carbon fiber and the connecting copper wire were stabilized by gluing them into a pulled-glass capillary before the electrode was cut with a scalpel to expose the electroactive disc at the tip. The resonance frequencies of the obtained electrodes varied in the range 1–5 kHz according to the length of the fiber protruding from the encasing glass capillary.

The electrochemical quality of the obtained carbon-fiber microelectrodes has been evaluated by cyclic voltammetry and by comparing theory versus their z -approach characteristics towards a nonconducting surface in the presence of a freely diffusing redox species, $[\text{Ru}(\text{NH}_3)_6]^{2+/3+}$ (Figure 2).^[15] The approach characteristics are consistent with a disk-shaped electrode surrounded by a thin insulating sheath.

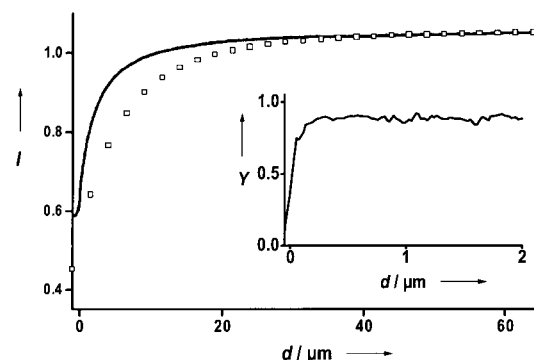


Figure 2. Approach characteristics of a carbon-fiber microelectrode to a glass surface. The obtained current response is compared against theory (rectangles) calculated for an electrode with a thick insulating sheath (tenfold radius of the conducting core). The inset displays the damping of the vibration amplitude multiplied by the sine of the phase shift (Y signal) caused by shear-force interaction with the glass surface. Redox mediator: 5 mM $[\text{Ru}(\text{NH}_3)_6]\text{Cl}_3$; electrode potential: -300 mV versus Ag/AgCl ; electrode radius: 3.5 μm .

These optimized carbon-fiber microelectrodes have been applied to the visualization of the topography of adherently growing PC12 cells. Using the shear forces occurring between the vibrating carbon-fiber electrode and PC12 cells, repositioning the tip is possible and a topographic image is obtained by drawing the z -displacement over the x,y -position of the tip (Figure 3).

Evidently, the interaction forces between the carbon-fiber tip and the sample are sufficiently small to allow the shear-force mode to be applied for visualizing the topography of individual living cells. For this, the tip is kept at a constant small distance over the cell membrane during scanning and, simultaneously, the microdisk surface can be used to detect changes in the concentration of redox-active compounds invoked by the metabolic and secretory action of the cell. Moreover, one may select specific sites at a single cell for perpendicular positioning of the microelectrode in order to monitor changes of the concentration of redox-active species

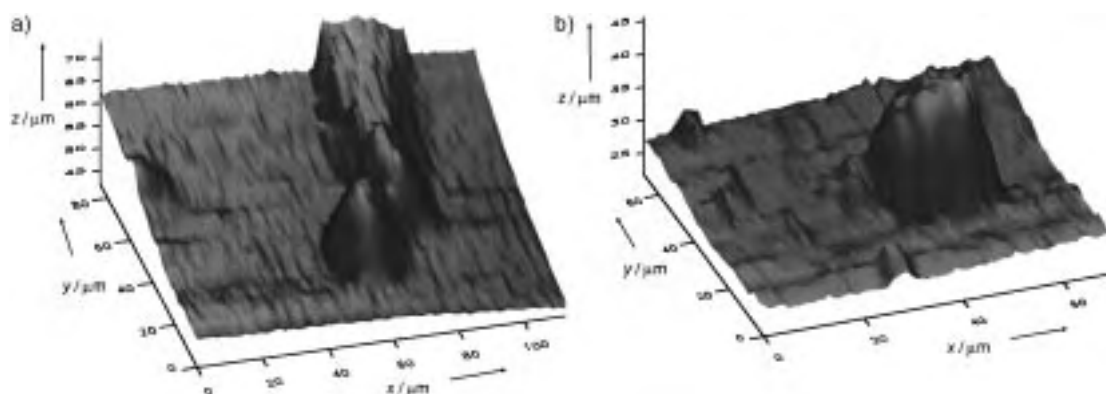


Figure 3. Shear-force based imaging of biological samples with carbon fiber electrodes with optimal stiffness (carbon-fiber microelectrode of diameter about 10–12 μm). a) Topography of a group of PC12 cells with an individual cell in the front. b) Topographic image of an individual PC12 cell.

with time. The discrete release of hormones and neurotransmitters from cells during exocytosis events is of especial interest to gain increased insights into cell–cell communication processes.

In a typical experiment, an adherently growing single cell is identified by means of a high resolution video microscope integrated within the SECM setup. After a coarse approach of the carbon-fiber microelectrode to the cell, the shear-force positioning starts and the topography of the cell is visualized (Figure 4a). The scanning procedure is then stopped at a

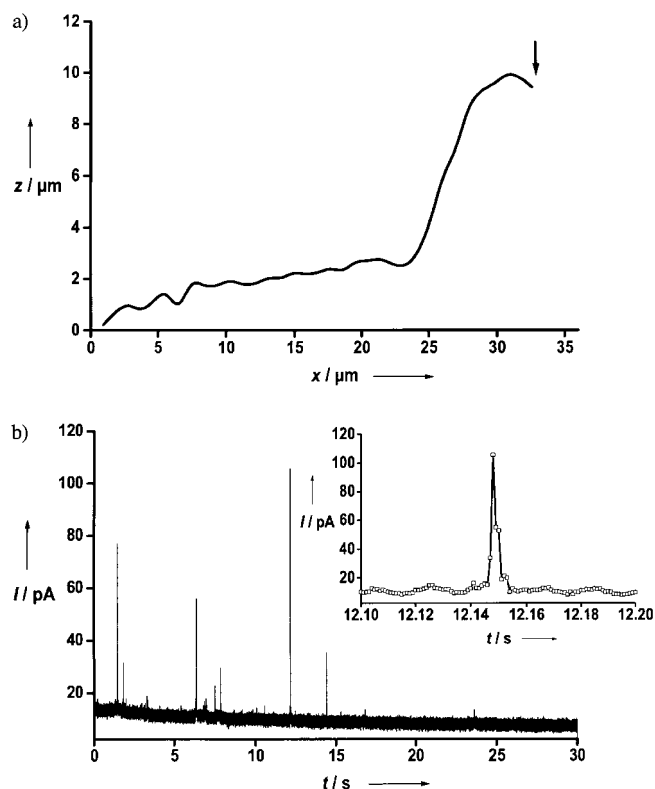


Figure 4. a) Adjusting the position of the microelectrode during scanning over a single PC12 cell. The arrow marks the final electrode position prior to the detection of discrete neurotransmitter release. b) Recording of single exocytotic events at a PC12 cell after application of K^+ ions. The inset shows the time course of the oxidation current with an expanded time scale of a selected single event. Electrode potential: +700 mV versus Ag/AgCl; data acquisition rate: 1000 Hz; tip diameter 10–12 μm.

defined site of interest (such as at the center of the cell). A small glass capillary, which is connected to a liquid-dispensing system, is positioned in close proximity to the selected cell and exocytosis is invoked by application of elevated K^+ concentrations through the positioned glass capillary. The increase of the K^+ concentration leads to a depolarization of the cell membrane causing an influx of Ca^{2+} ions followed by a reaction sequence which finally leads to the fusion of neurotransmitter-containing vesicles with the cell membrane, thus triggering the discrete release of the neurotransmitter molecules into the extracellular space. Due to the small gap between cell membrane and microelectrode tip, the released neurotransmitter molecules are consumed at the electrode which is poised to a constant potential of 700 mV versus Ag/AgCl using a high-sensitive potentiostat. This electrode potential is sufficiently high to oxidize the released neurotransmitter (in the case of PC12 cells, a mixture of the catecholamines adrenaline, noradrenaline, and dopamine). The oxidation current recorded during the single vesicle exocytosis is monitored using fast data-acquisition software (Figure 4b).

Due to the size of the electrode disk and the very short gap between the cell membrane and the microelectrode, a 100% collection efficiency can be assumed if the release site at the cell is positioned opposite the microelectrode center. Although electrode fouling may occur due to subsequent reactions of the primarily oxidized neurotransmitter molecules, the charge transferred during the exocytotic event is related to the number of molecules released by the cell. Either a sequence of events can be recorded with the microelectrode kept at the same position or, after a rest period and repositioning of the microelectrode over a different spot of the cell, exocytosis can be invoked again providing a sufficiently small increase of the K^+ concentration after the first depolarization process within the electrolyte solution.

The implementation of carbon-fiber based electrodes in a SECM in combination with a shear-force based distance regulation represents a significant advance for the application of electrochemical scanning probe techniques to fragile biological systems with complex three-dimensional structures. The optimized microelectrodes are suitable for combined topographical and electrochemical studies of soft biological

preparations using a shear-force dependent height-control system. Based on the topographical data, regions of interest on the cell membrane can be identified and spatially addressed with the microelectrode. Current work is directed towards a further decrease of the diameter of the used microelectrodes to submicrometer dimensions and the precise positioning of these fragile microelectrodes in close proximity to individual cells using shear-force interactions. In principle, the application of such miniaturized microelectrodes should allow elucidation of metabolic reactions even at substructures of cells.

Experimental Section

SECM: The SECM with integrated height control and video microscope has been described elsewhere.^[10] All electrochemical measurements were carried out using a VA-10 potentiostat (npi electronic GmbH, Tamm, Germany) and an AgCl-coated silver wire as pseudo reference electrode.

Polymer-insulated carbon-fiber electrodes: A single carbon fiber (SGL Technik GmbH, Meitingen, Germany) of diameter 7 μm and length 15 mm was connected to a copper wire by means of silver epoxy glue (H20, EpoTek, Walldbronn, Germany). Parts of the copper wire and the fiber were inserted into a glass capillary and fixed with glue. The capillary was pulled around the fiber with a standard pulling apparatus (Narishige Model PP 830, Science Products, Hofheim, Germany). The electrodeposition was performed as described elsewhere.^[13] The fiber was dipped into insulating paint (RS Components, Corby, Northants, UK) and allowed to dry at least 1 h. The ratio of insulator thickness to the fiber radius varied between 0.25–1 depending on the amount of coating cycles. Cyclic voltammetry was used to assure the quality of the obtained insulation. A carbon disc was exposed by cutting the insulated fiber with a scalpel. The microelectrode was inspected under the microscope for a smooth cutting and further characterized by means of cyclic voltammetry.

Retzius cells from medicinal leeches were dissected and cultured as described previously.^[16] PC12 cells were grown on poly(ornithine)-covered glass slides following a procedure described elsewhere.^[17]

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“Supramolecular” Solid-State Chemistry: Interpenetrating Diamond-Type Frameworks of U^{4+} Ions Linked by S,S' -Bidentate $\text{P}_2\text{S}_6^{2-}$ Molecular Rods in $\text{UP}_4\text{S}_{12}^{**}$

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Organic compounds can self-assemble into ordered arrays at low temperature that are capable of molecular recognition, and that can act as biomimetic systems.^[1] As a result, organic supramolecular chemistry has afforded many intriguing results,^[2] including various three-dimensional (3D) hydrogen-bonded frames of super-diamond-type^[3] and super-wurtzite-type structures.^[4] In the field of inorganic and coordination polymers, Hoskins and Robson^[5] have proposed a strategy for the design of new 3D phases, referred to as

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“scaffolding-like materials”, which are assembled by using suitable metal centers (e.g. with tetrahedral, square-planar, or octahedral connectivity) and rodlike or platelike molecular building blocks of different nature and length. This rational has been applied to the synthesis of a number of new compounds, whose structures exhibit interwoven nets.^[6–8] Each of a number of simple structures (e.g. diamond, PtS, α -Polonium) may be regarded as prototype for a whole family of new frameworks in which bonds of the parent structure are replaced by a range of molecular rods. Simple bidentate linear ligands with different rod lengths are attractive rodlike connectors.^[9] In some cases these polymeric structures evolve as single infinite frameworks leaving relatively large cavities and/or channels; in others, such as in $\text{Zn}(\text{CN})_2$,^[10] the cavities are filled by one or more identical independent frameworks. Corresponding advances in solid-state reactions have been confined to few examples such as $[\text{Ph}_4\text{P}]_2[\text{M}(\text{Se}_6)_2]$,^[11] $\text{K}_2\text{PdSe}_{10}$,^[12] or $\text{Ta}_4\text{P}_4\text{S}_{29}$.^[13]

Based on the observation that PS_4 and P_2S_6 groups can act as mono-, bi-, or tridentate ligands in early transition metal thiophosphates^[14] and the fact that even high coordination numbers of metals such as niobium or uranium can provide low connectivities with chelating ligands, we explored the quasibinary system $\text{US}_2/\text{P}_2\text{S}_5$ for new compounds containing uranium coordinated by PS_4 , P_2S_6 , or $\text{S}_3\text{P}(\text{S})\text{PS}_3$ groups. Herein we report the synthesis and structural characterization of $\text{U}(\text{P}_2\text{S}_6)_2$ (**1**), a compound with a three-dimensional architecture composed of three interpenetrating SiO_2 -type frameworks. The extended structure may be rationalized based on the length of the P_2S_6 connecting rods.

Compound **1** was synthesized in the solid-state reaction of U, P_2S_5 , and S in a 1:2:2 ratio at 700°C .^[15] Single crystals were obtained by annealing followed by slow cooling to room temperature. Compound **1** crystallizes in the tetragonal space group $I4_1/a$ with two formula units per cell. The structure^[16] of **1** contains three interpenetrating diamond-type frameworks, based on elongated adamandoid cages (Figure 1). The length of shortest vector relating the three independent networks is

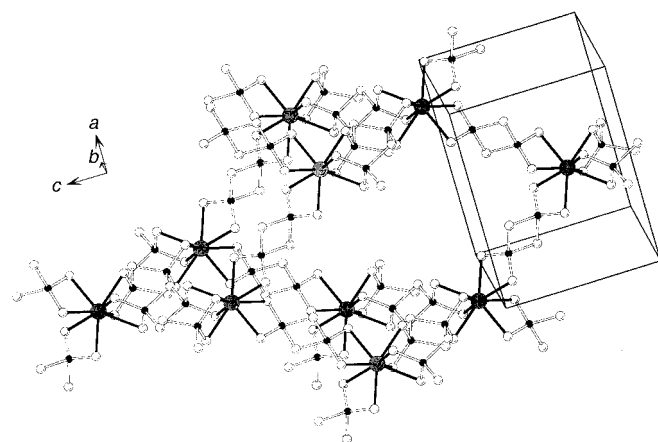


Figure 1. A view of a single adamantoid cage of **1** (U: gray spheres; P: black spheres; S: white spheres). Atom positions ($x, y, z, U_{\text{eq}} \times 10^3$): P(1) 0.0062(1), 0.0662(1), 0.3808(1), 113(1); S(1) 0.1681(1), 0.1840(1), 0.6774(1), 117(1); S(2) 0.1195(1), 0.1681(1), 0.3480(1), 119(1); S(3) $-0.1812(1), -0.1557(1), -0.0238(1), 16(1)$ U 0 $1/4, 1/8, 11(1)$. Selected distances [$\text{\AA}$]: U–S(2) 2.879(1) ($4 \times$), U–S(3) 2.812(1) ($4 \times$), P–S(1) 2.107(2), P–S(1) 2.113(2), P–S(2) 1.989(2), P–S(3) 1.997(2).

9.75 $\text{\AA}$. The U atoms are coordinated by eight S atoms of four bidentate P_2S_6 ligands in a square-antiprismatic fashion leading to a pseudotetrahedral arrangement of the dithiophosphate groups. The metal atoms are located on S_4 axes of the cell and display crystallographically imposed D_{2d} coordination symmetry. Each uranium atom has a slightly distorted square-antiprismatic coordination environment (the distortion being caused by $\text{S} \cdots \text{S}$ repulsion between the P_2S_6 units) with S(2)–U–S(3) angles of $69.96(3)^\circ$ for the S atoms of each P_2S_6 ligand. The U–S and P–S distances are unexceptional; selected values are compiled in the caption of Figure 2. The S(2)–P–S(3) bite angle of $109.90(8)^\circ$ and the bridging U–S–P angles of $88.47(5)^\circ$ and $90.23(5)^\circ$ are consistent with the presence of essentially planar US_2P rings. The P–U–P angles of $86.54(1)^\circ$ ($2 \times$) and $122.02(1)^\circ$ ($4 \times$) indicate a compression of the $\text{U}(\text{S}_2\text{PS}_2)_4$ “pseudotetrahedron” in accordance with a c/a ratio of 0.76.

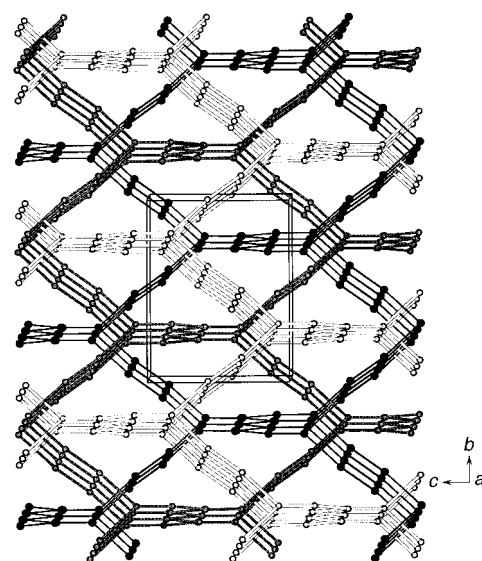


Figure 2. A schematic view of the three equivalent interpenetrating diamondoid frameworks in **1**. The P_2S_6 groups are represented by rods connecting the P atoms of the P_2S_6 ligands.

The title compound **1** is a novel member of the family of super-diamond networks in coordination chemistry. Although there is little precedent in metal/chalcogenide systems, the structure of **1** is closely related to that of methane tetraacetic acid.^[18] Interpenetration, which arises by the necessity to fill empty space inside the large cages, is the rule rather than the exception in these species. The structural variability is large, including the presence of different interpenetrating frames, different types of tetrahedral centers, anisobidentate ligand, mixed rods, chiral metallic centers, and polymetal centers.

In an undistorted (cubic) diamond network each adamantane-type unit possesses three mutually perpendicular inversion axes running parallel to the cubic axes of the unit cell. The three interwoven diamond-type networks are oriented in such a way that the nodes of the independent frames are oriented along these inversion axes with identical interframe separations. This is illustrated schematically in Figure 2 for the title compound **1**. Here the frames of two further

independent nets are located between the upper and lower frame. Furthermore, it is apparent that the frames are distorted in such a way that the adamantane-type units are elongated along one of the S_4 axes; this reduces the symmetry of the structure from cubic to tetragonal. The distance between the uranium atoms in the 3D framework structure determines the size of the adamantane-type cage. To optimize space filling by stuffing empty space in the structure, independent frameworks arrange themselves in such a way as to fill each other's empty cages and tunnels. As an example, Si...Si distances of 6.8 Å between the tetrahedral centers in $\text{Si}(\text{NCN})_2$ ^[19] are compatible with two interpenetrating diamond-type networks, whereas U...U separations of 9.75 Å in **1** require three interpenetrating frameworks for optimum space filling. Rodlike ligands with exceptional length such as 4,4'-biphenyldicarbonitrile (PCN) in $[\text{Ag}(\text{BPCN})_2]\text{PF}_6$ ^[20] can lead to the formation of a ninefold interwoven diamond-type network with distances of 16.42 Å between the metal centers.

Based on a formal assignment of oxidation states the electronic structure of **1** can be represented by $(\text{U}^{4+})(\text{P}^{5+})_4(\text{S}^{2-})_{12}$. From this formula, an f^2 system with two unpaired electrons may be expected. The molar magnetic susceptibility χ_{mol} of **1** was measured as a function of temperature (4–300 K). The effective magnetic moment μ_{eff} of $3.84 \mu_{\text{B}}$ at 300 K is consistent with an f^2 configuration.^[21] The magnetic susceptibility of **1** follows a Curie–Weiss type behavior with $C = 3.14 \text{ cm}^3 \text{ K mol}^{-1}$ and $\theta = -270.6 \text{ K}$, as apparent by the shape of the $1/\chi_{\text{mol}}$ versus T and μ_{eff} versus curves (Figure 3). The large negative value of θ indicates that

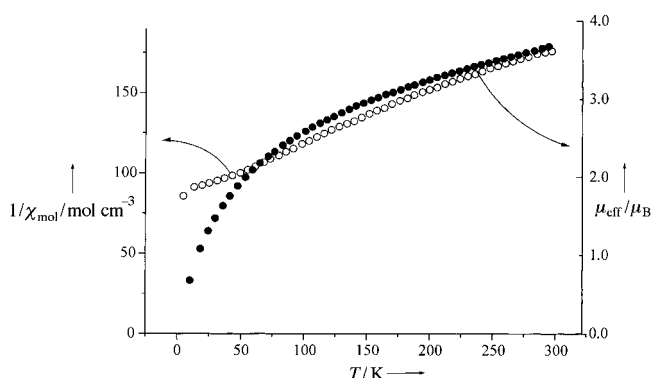


Figure 3. Temperature dependence of $1/\chi_{\text{mol}}$ (○) and μ_{eff} (●) for **1**.

antiferromagnetic interactions prevail, although no antiferromagnetic ordering is observed down to 4 K. These observations are in agreement with uranium centers which are magnetically coupled through the P_2S_6 ligands. Magnetic through-bond coupling through five and more atoms is not unusual and has been reported for a number of coordination compounds^[22] or electrosodalites.^[23] Furthermore, through-space coupling over distances as large as 8 Å has been observed in fullerenes.^[24] On the other hand, nonmagnetic f^2 ground states in U^{4+} compounds are not known to the best of our knowledge, whereas antiferromagnetic transitions have been observed in many other uranium compounds,^[25] although in several cases the data analysis is complicated by the presence of additional 3d metals.^[26]

In conclusion, the formation of **1** indicates that interpenetrating framework structures can also be formed in high-temperature solid-state reactions, which are not in the realm of conventional coordination chemistry or soft-chemistry low-temperature approaches. Since the deliberate use of “solid state” ligands is difficult to achieve in high-temperature reactions, only a few examples such as $\text{Ta}_4\text{P}_4\text{S}_{29}$,^[13] $\text{ATi}_2(\text{PS}_4)_3$ ($A = \text{Li}, \text{Na}$),^[27] $\text{Cr}_3\text{P}_3\text{S}_{9+x}$,^[28] or $\text{Li}_9\text{B}_{19}\text{S}_{33}$ ^[29] have been reported so far; nevertheless, a variation of the thiophosphate ligand by deliberate choice of composition and temperature allows the synthesis other framework structures. Apparently, the combination of properties such as rigidity, coordination behavior, ligand dimensions, or thermal stability allows the use of the thiophosphate moieties for the synthesis of “supramolecular” solid-state aggregates.

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- [16] Data were collected in on a Siemens (Bruker) SMART platform with a CCD detector using monochromated MoK_α radiation ($\lambda = 0.71073 \text{ Å}$) over more than a hemisphere of reciprocal space ($2\theta < 55^\circ$). Crystal data: UP_4S_{12} , $M_f = 746.63$, tetragonal, space group $I4_1/a$ (no. 88), $a = 12.8776(9)$, $c = 9.8367(10) \text{ Å}$; $V = 1631.25 \text{ Å}^3$, $Z = 4$,

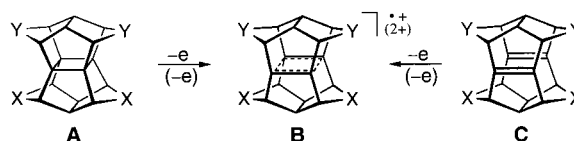
$\rho_{\text{calc}} = 3.040 \text{ g cm}^{-3}$, $\mu = 11.85 \text{ mm}^{-1}$. Crystal size $0.08 \times 0.08 \times 0.2 \text{ mm}^3$. The SMART software was used for data acquisition and the SAINT software for data extraction.^[17a] Unit cell parameters based on 25 reflections ($12^\circ < 2\theta < 30^\circ$). Absorption correction by SADABS,^[17a] structure solved and refined by using the SHELXS-86^[17b] and SHELXTL program systems,^[17c] 1003 independent reflections, 913 with $F > 4\sigma(F_o)$, $R = 0.032/wR2$ (all data) = 0.061; max./min. residual electron density $2.2/-1.3 \text{ e } \text{\AA}^{-3}$ in the vicinity of the U atoms. 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-411668.

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σ -Bishomoconjugation (σ -Bishomoaromaticity) in 4C/3(2)e Cations—Scope and Limitations**

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The experimental verification of σ -bishomoconjugation (σ -bishomoaromaticity) in the 4C/3e radical cation and the 4C/2e dication **B**, generated by one- and two-electron oxidation of the [1.1.1.1]pagodane **A** ($X = Y = \text{CH}_2$) and of the respective [1.1.1.1]pagodadiene **C** (“biseco-dodecahedradiene”), respectively, was a prominent spin-off from our search for versatile synthetic routes to pentagonal dodecahedranes.^[1] In order to



assess the geometrical prerequisites of these novel bonding motifs,^[2] modification of the cage structures has been pursued in three directions: a) by formal rotation of a molecular “half” ($\rightarrow$ “isopagodanes”),^[3] b) by homologation at the X- and/or Y-positions ($\rightarrow$ [2.2.1.1]/[2.2.2.2](iso)pagodanes),^[3] and c) by bridging the X,Y positions ($\rightarrow$ (homo)dodecahedradienes).^[4] A particularly attractive triad of this latter series consists of the parent biseco-(**1**), seco-(**2**), and 1,16-dodecahedradienes (**3**) (Scheme 1).^[5]

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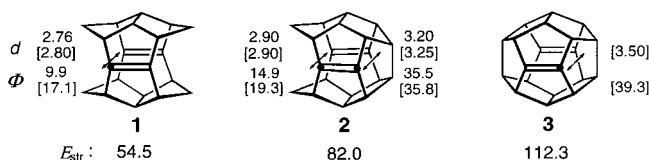
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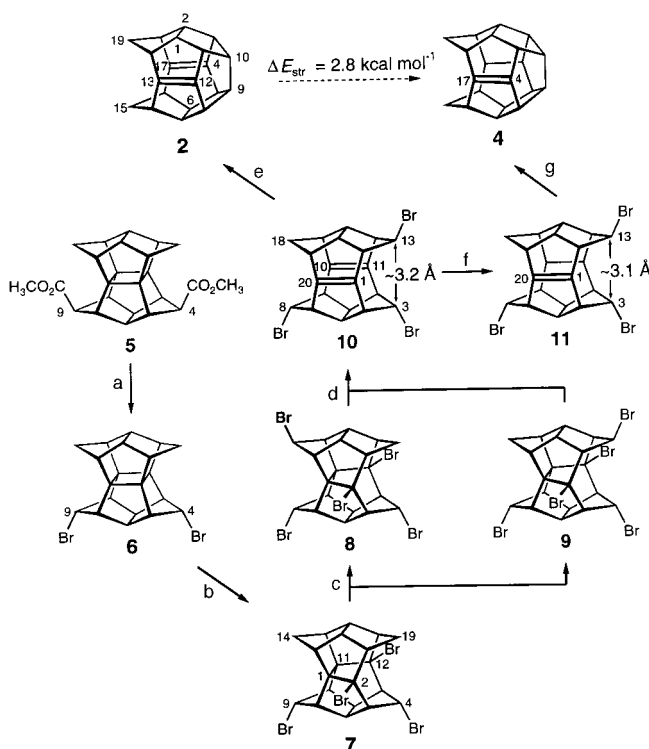
[**] This project has been supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and BASF AG. We thank A. Kurscheidt and M. Lutterbeck for technical assistance, Dr. D. Hunkler and Dr. J. Wörth for NMR and MS measurements, and Prof. Dr. T. Bally for access to his ^{60}Co - γ -irradiation equipment.



Scheme 1. Experimental and calculated (B3LYP/6-31G*, in square brackets) π,π -distances d [Å], pyramidalization angles Φ [°], and strain energies E_{str} (MM3, [kcal mol⁻¹]).

For very “proximate” **1**, it had been established that radical cation **1**^{•+} and dication **1**²⁺ are persistent even at room temperature, whilst for “distant” **3** the radical cation **3**^{•+} does exist only in a low temperature matrix and dication **3**²⁺ is not observable at all.^[6] The synthesis of the missing compound **2**—the “hybrid” of **1** and **3** with regard to its π,π -distances d and pyramidalization Φ on the olefinic carbon atoms^[7]—and of monoene **4** as a reference, as well as their response to one-/two-electron oxidation are subject of this Communication.

Prior attempts to prepare parent **2** through defunctionalization of available derivatives^[7, 8] have consistently failed due to the incompatibility of the severely bent C–C double bonds with the respective reaction and separation conditions. Success came with the reaction sequence shown in Scheme 2 (total yield of **2** > 30% with only 5–6% of **1** as impurity),^[9, 10] when a satisfying protocol for the problematic step **10**→**2**—internal competition between reductive C3–C13 bond formation and hydrogenolytic C–Br cleavage—had become



Scheme 2. a) 1) KOH, HOCH₂CH₂OH, 180 °C, 16 h; 2) H₂O, conc. HCl; 3) 2-mercaptopyridine-1-oxide (Na salt), DMAP, BrCCl₃, 120 °C, 30 min; 76%. b) Br₂/CH₂Cl₂ (10/1), RT, *hν* (300 W daylight lamp), 5 min; > 95%. c) Br₂/CH₂Cl₂ (4/1), RT, *hν* (300 W daylight lamp), 5 h; 95%. d) KI, DMF, 180 °C; 70%. e) 1) Li/Hg, THF, –78 °C→RT, 2 h; 2) MeOH, 1 h; 80–85%. f) N₂H₄, 0 °C, 12 h; 95%. g) 1) Li/Hg, THF, –78 °C→RT, 2 h; 2) MeOH/1 h; 80–85%. DMAP = 4-dimethylaminopyridine.

available after intensive experimentation with various metals and electron-transfer agents.

For the hydrogenation of diene **2** to monoene **4**, only a small increase in strain was calculated (+2.8 kcal mol⁻¹); correspondingly, the selective preparation of **4** through hydrogenation of **2** was found to be not possible. Alternatively, **4** was expeditiously obtained by hydrogenation of tribromobiseco-diene **10** to give “hyperstable”^[11] **11** followed by cyclization.

The longest wavelength UV/Vis absorption of **2** at 254 nm ($\epsilon \approx 600$, *n*-hexane), as evidence for transannular π,π -interaction (charge transfer), hardly differs from that of **3** (252 nm, $\epsilon \approx 350$) but significantly from that of **1** (270 nm, $\epsilon = 180$). In the ¹³C NMR spectra, the olefinic shifts of 151.8 and 171.4 ppm reflect the degree of pyramidalization, while $\Delta\delta = 1.47$ for the geminal methylene protons reflects the steric constraint inside the half-cage.^[7]

In the photoelectron (PE) spectrum of **2**, the mean value (8.06 eV) of the two π -ionization bands (7.48 and 8.64 eV) turns out to be higher by 0.15 eV than the π -band of **4** (7.91 eV). The π,π -split ($\Delta_{\pi\pi}$) of 1.16 eV is well reproduced by calculations (B3LYP/6-31G*: 1.14 eV; AM1: 1.03 eV). According to Heilbronner–Schmelzer analysis, 87% of the split is caused by through-space (TS) interaction (compare **1**: $\Delta_{\pi\pi} = 1.91$ eV, 100% TS and **3**: $\Delta_{\pi\pi} = 0.68$ eV, 59% TS).^[12]

Cyclovoltammetry (CH₂Cl₂, *n*Bu₄NPF₆, –20 °C, 0.2 V s⁻¹) recorded two irreversible oxidation waves with $E_p = 1.00$ and 1.50 V for **2** and one irreversible wave with $E_p = 1.60$ V for **4** (**1**: $E_{1/2} = 0.66$ V, $E_p = 1.20$ V; **3**: $E_p \approx 1.0$ V). The difference of the peak potential for **2**^{•+} relative to **4**^{•+} ($\Delta E_p = 0.60$ V) as a measure for the homoconjugational stabilization of **2**^{•+} has to be compared with $\Delta E_p = 0.91$ V for **1**^{•+} and $\Delta E_p \approx 0.4$ V for **3**^{•+} relative to the respective monoenes.^[13]

The radical cation **2**^{•+} could not be observed after oxidation of **2** in fluid solution as established for **1** (AlCl₃, tris(*p*-bromophenyl)ammoniumyl hexachloroantimonate, Ti(O₂C–CF₃)₃, electrolysis).^[5] However, as for **3**,^[6] γ -irradiation of **2** and **4** in a CFCl₃ matrix allowed the observation of ESP spectra (Figure 1). The pattern of the ESP spectrum attributed to **2**^{•+} is dominated by a nonet spaced by about 1.5 mT (eight nearly equivalent protons, no differentiation between the β/β' protons). Additional information follows from the polarization pattern of the CIDNP experiment, in which **2**^{•+} was generated by photoinduced electron transfer to chloranil (tetrachloro-*p*-benzoquinone, in CD₂Cl₂). From the intensities of the two emissions lines at 3.28 and 3.48 mT, ¹H hyperfine coupling constants (hfc) of 1.18 and 1.55 mT for the β and β' protons were derived.^[14] These values are in very good agreement with the calculated (B3LYP/6-31G*[¹⁵]) ¹H hfc of 1.49 (β) and 1.59 mT (β'); the very small hfc for the remaining protons (<0.1 mT) are not resolved in experimental spectra.

In the case of **4**^{•+}, the ESP spectrum reveals a pattern due to two pairs of equivalent protons with ¹H hfc of 4.3 and 2.9 mT (Figure 1). According to the calculated values of 3.98 and 2.71 mT, these hfc are attributed to the β and β' protons.

In line with the cyclically delocalized 4C/3e configuration of **2**^{•+}—within the ESP time scale—these hfc are about one half those of **4**^{•+}. According to calculations, in the trapezoidal 4C/3e structure of **2**^{•+} the C_{2v} symmetry of parent

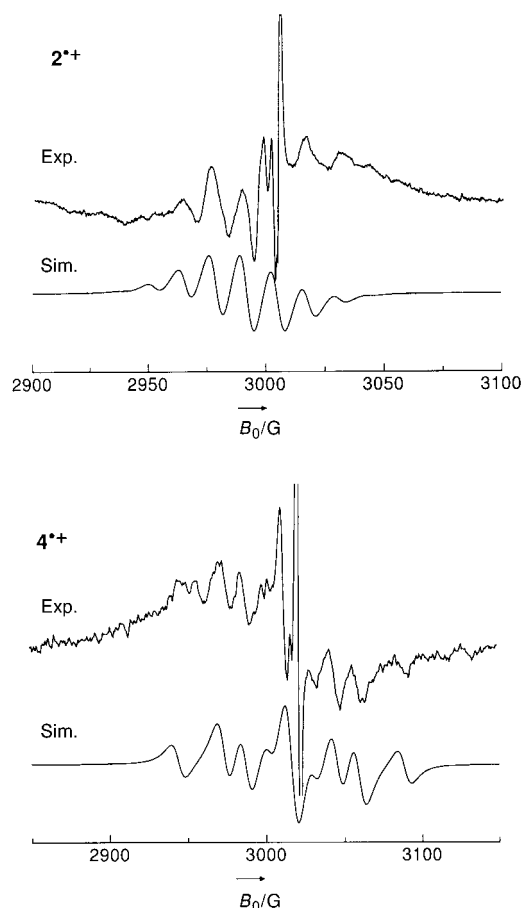
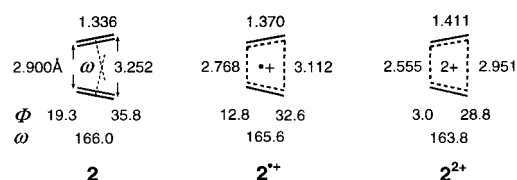


Figure 1. ESR spectra of **2** and **4** (CFCl₃, 100 K, modulation 0.5 mT).

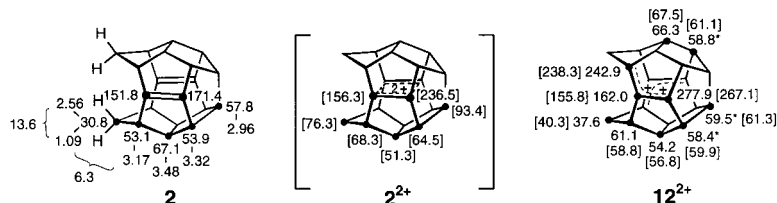
2 is retained, the C–C double bonds are lengthened by 0.034 Å, and the π,π -distances are shortened by 0.132/0.140 Å (Scheme 3).



Scheme 3. Calculated structures of diene **2**, in-plane homoconjugated radical cation **2⁺**, and σ -bishomoaromatic dication **2²⁺** (B3LYP/6-31G*; distances d [Å], pyramidalization angles Φ [°], and angles ω [°]).

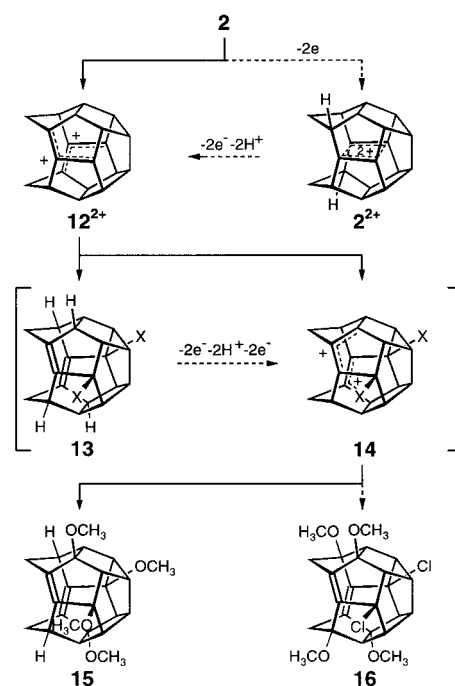
For its two-electron oxidation, **2** was mixed (as a slurry in SO₂ClF at –70 °C) with a six-fold excess of SbF₅ in SO₂ClF at –70 °C. After very slow dissolution (vortex stirrer, –70 °C), a dark yellowish-brown solution developed. At this temperature, the NMR signals were quite broad and indicate some paramagnetic species. Upon warming to –20 °C, however, the peaks sharpened. Whilst the ¹H NMR spectrum was too complex to allow an interpretation, the ¹³C NMR spectrum clearly revealed the presence of one prominent species (>80%, ten intense signals and several weaker ones). The assignment to C₂ symmetrical bisallylic dication **12²⁺**, rather than to the C_{2v} symmetrical 4C/2e dication **2²⁺**, is based on the

number of ¹³C NMR signals (ten rather than seven), the allylic nature of the three olefinic signals (δ = 277.9, 242.9, and 162.0; Scheme 4), and the good agreement with the GIAO-B3LYP/6-31G* calculations.^[16] Additional support comes from



Scheme 4. Experimental and calculated (GIAO-B3LYP/6-31G*, in square brackets) ¹³C NMR shifts δ for dications **2⁺** and **12²⁺**. For comparison, ¹H and ¹³C shifts and $J(\text{H,H})$ coupling [Hz] for diene **2** (C₆D₆) are given.

quenching the superacid solution with CH₃OH/Na₂CO₃. Two main products could be chromatographically separated from a complex mixture of mostly higher methoxylated dienes (MS, $\approx$ 25%), unequivocally identified as C₂-symmetrical tetramethoxydiene **15** ($\approx$ 30%) and C₂-symmetrical dichlorotetramethoxydiene **16** ($\approx$ 25%). The intermediacy of dienes **13** (X = OCH₃, Cl) and bisallylic dications **14** (X = OCH₃, Cl) is



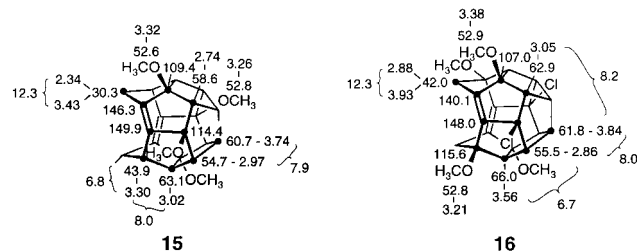
plausible. Correspondingly from DFT calculations, the parent diene structure **13** (X = H), and not **2**, had surfaced as “stabilomer” of the seco-dodecahedradiene family (–3.5 kcal mol^{–1} versus **2**). An intriguing cascade of oxidation/deprotonation/OCH₃-addition steps during the quenching procedure is held responsible for the C₂₀H₄(OCH₃)₁₄ ion in the MS spectrum (m/z = 678, low intensity) and suggests the total substitution of all tertiary hydrogens by CH₃O groups.

The radical cation generated from diene **2** in low temperature matrices (or with very short lifetime in solution, CIDNP), is firmly established as in-plane cyclically delocal-

ized 4C/3e species. Both, the total π, π split (PE) as well as its through-space/through-bond partition, the degree of homo-conjugational stabilization (cyclovoltammetry), and the structural details (DFT) place 2^{++} between 1^{++} and 3^{++} . A limitation of the observability of σ -bishomoaromatic 4C/2e dications is manifested: If 2^{2+} is an intermediate at all on the way from 2 to 12^{2+} , minimization of Coulomb repulsion through “hydride” elimination^[17]—prohibited by the skeleton in 1^{2+} (“anti-Bredt protection”)^[18]—wins over σ -bishomoaromaticity.

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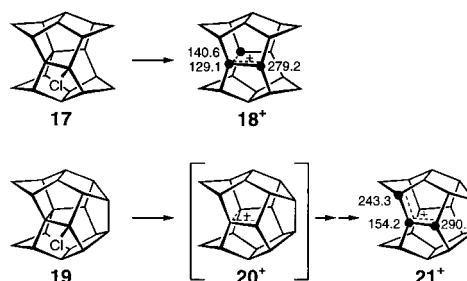
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A Versatile and High-Yield Route to Active and Well-Defined Catalysts [Ru(bisphosphane)(H)(solvent)₃](BF₄)⁺

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Valentin Rautenstrauch*

The well-known and well-defined Rh systems $[\text{Rh}(\widehat{\text{P}}\text{P})(\text{sol})_2]^+$ ($\widehat{\text{P}}\text{P}$ = chiral bisphosphane ligand, sol = weakly O-bound solvent, for example acetone, THF, MeOH)^[1] catalyze a wide variety of reactions, the most prominent of which is the asymmetric hydrogenation of functionalized

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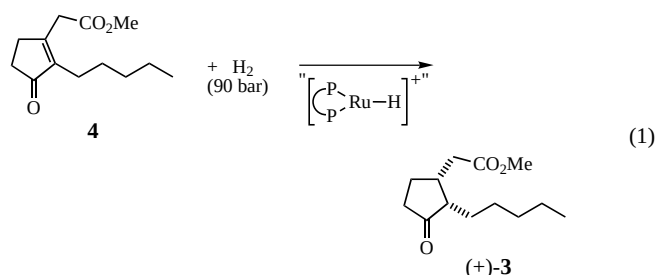
alkenes. The latter reaction is the most-studied reaction in enantioselective catalysis and has attained a high degree of maturity.^[2] The versatility and efficiency of these catalysts arises to a large part from a combination of three features. They are generated cleanly and in high yield, maximizing their net activities. They readily undergo insertion reactions, two-electron oxidative additions, and reductive eliminations. They are coordinatively unsaturated, contain labile solvent ligands, and are sterically unencumbered. This combination of coordination unsaturation and low steric congestion accommodates reactions that proceed by oxidative addition of H–X (e.g. X = H for hydrogenation) as well as alkene or ketone coordination.

In the mid 1980s, the focus changed from Rh to lower costing Ru, and it is now evident that the most versatile and often the most active chiral catalysts for hydrogenation of functionalized alkenes and ketones are $[\text{Ru}^{\text{II}}(\text{P}^{\text{P}})]$ complexes.^[2] Despite this, only two of the Ru systems known prior to the present work^[3] possess features that parallel those of $[\text{Rh}(\text{P}^{\text{P}})(\text{sol})_2]^+$, and the importance of these two may have been overlooked. Both are hydrido, monocationic complexes of the type $[\text{Ru}(\text{P}^{\text{P}})(\text{H})(\text{sol})_n]^+$ ($n = 2, 3$). These cations also possess a hydride ligand, which allows for reaction pathways not directly available in the Rh systems.

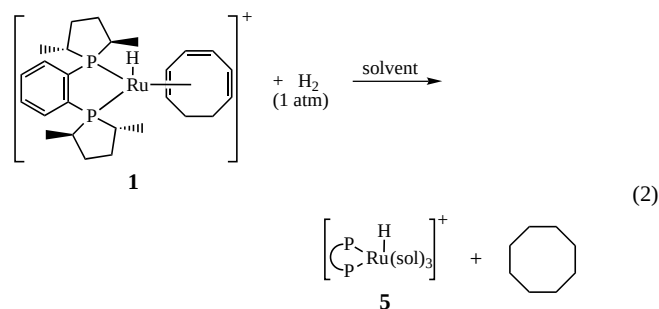
The first such system, reported by the group of one of us,^[4] consists of the compounds $[\text{Ru}(+)-\text{BINAP}(\text{H})(\text{MeCN})_n(\text{sol})_{3-n}](\text{BF}_4)^{[5a]}$ ($\text{sol} = \text{MeOH}, \text{THF}, \text{acetone}, n = 0-3$), which catalyze the hydrogenation and hydrosilylation of functionalized C–C and ketonic C–O double bonds as well as the isomerization of olefins.^[4a,c] Access to the system^[4a] was established by treating the known *cis*- $[\text{Ru}(1,2:5,6-\eta\text{-cod})(\eta^3\text{-allyl})(\text{MeCN})_2](\text{BF}_4)^{[6]}$ ($\text{cod} = 1,5\text{-cyclooctadiene}$) with (+)-BINAP to give $[\text{Ru}(+)-\text{BINAP}(1,2,3:5,6-\eta\text{-C}_8\text{H}_{11})(\text{MeCN})](\text{BF}_4)$ ($\text{C}_8\text{H}_{11} = 2,5\text{-cyclooctadienyl}$). Hydrogenation at atmospheric pressure and room temperature generates cyclooctane and $[\text{Ru}(+)-\text{BINAP}(\text{H})(\text{MeCN})_n(\text{sol})_{3-n}](\text{BF}_4)$. Since the MeCN ligand effectively blocks one coordination site, one could expect $[\text{Ru}(\text{P}^{\text{P}})(\text{H})(\text{sol})_n]^+$ to be much more active in the absence of MeCN or other strongly coordinating solvents. The second of such species was reported by Pregosin et al.^[7] The coordinatively unsaturated $[\text{Ru}(-)-\text{di-}i\text{Bu-MeOBIPHEP}(\text{H})(i\text{PrOH})_2](\text{BF}_4)^{[5b,7]}$ was generated from the corresponding Takaya–Noyori precursor $[\text{Ru}(-)-\text{di-}i\text{Bu-MeOBIPHEP}(\text{OAc})_2]^{[8]}$ by treatment with aqueous HBF_4 in *i*PrOH under 60 atm of H_2 . It is presumably the active catalyst for Hoffmann–La Roche's unprecedented hydrogenation of a 2,5-dialkyl-3-hydroxy- α -pyrone.^[5b,7,9] Remarkably, this compound was characterized in the solid state by X-ray diffraction.^[7] Its synthesis is arduous and starts out from an advanced precursor, however, and there are no reports of analogues containing other P^{P} prepared by this procedure.

There are two reports on the dicationic complexes $[\text{Ru}(\text{P}^{\text{P}})(\text{sol})_4]^{2+}$, which have structures that more directly parallel $[\text{Rh}(\text{P}^{\text{P}})(\text{sol})_2]^+$. One is $[\text{Ru}(-)-\text{BINAP}(\text{MeCN})_4](\text{BF}_4)_2^{[10]}$ which is close to catalytically inactive, presumably because the MeCN ligands are bound too strongly. The other concerns a class of catalysts formulated at one time as “ $[\text{Ru}(\text{P}^{\text{P}})](\text{BF}_4)_2$ ” by the Hoffmann–La Roche group, but without structural characterization.^[5b,9]

Our previous paper^[3] describes the first synthesis of a new prototypal catalyst precursor, $[\text{Ru}((-)-\text{Me-DuPHOS})(\text{H})(\eta^6\text{-cot})](\text{BF}_4)$ (**1**; $\text{cot} = 1,3,5\text{-cyclooctatriene}$), made in one step from $[\text{Ru}(1,2:5,6-\eta\text{-cod})(\eta^3\text{-methallyl})_2]$, (–)-Me-DuPHOS^[5c] ((–)-**2**), and $\text{HBF}_4 \cdot \text{Et}_2\text{O}$. The catalyst precursor **1** was identified during the development of an industrial process for making the fragrance chemical (+)-*cis*-methyl dihydrojasmonate (+)-**3** by an enantioselective hydrogenation of the doubly functionalized, tetrasubstituted alkene **4**, a vinylogous β -oxoester [Eq. (1); the counterion BF_4^- is omitted throughout].



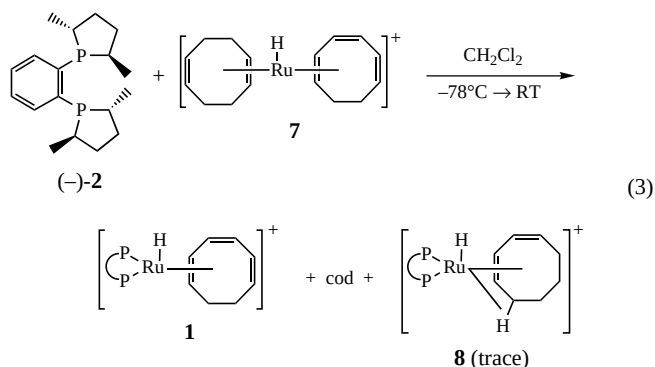
We found that **1** reacts cleanly within minutes at ambient temperature with H_2 at atmospheric pressure in the appropriate solvent to afford the catalysts *fac*- $[\text{Ru}((-)-\text{Me-DuPHOS})(\text{H})(\text{sol})_3](\text{BF}_4)^{[11]}$ (**5**; $\text{sol} = \text{acetone}, \text{MeOH}, \text{EtOH}$) and cyclooctane [Eq. (2)]. These results suggested that the



catalysts $[\text{Ru}(\text{P}^{\text{P}})(\text{H})(\text{sol})_3]^+$ are generally accessible from the precursors $[\text{Ru}(\text{P}^{\text{P}})(\text{H})(\eta^6\text{-triene})]^+$ by hydrogenation, just as $[\text{Rh}(\text{P}^{\text{P}})(\text{sol})_2]^+$ are accessed from $[\text{Rh}(\text{P}^{\text{P}})(\eta^4\text{-diene})]^+$.^[1,2]

Our first route^[3] to $[\text{Ru}(\text{P}^{\text{P}})(\text{H})(\eta^6\text{-cot})](\text{BF}_4)$ is difficult to adapt to P^{P} other than Me-DuPHOS (**2**). We thus sought a more general, simple, and high-yielding synthesis. As reported by Chaudret and Tkatchenko et al.,^[12] protonation of $[\text{Ru}(1,2:5,6-\eta\text{-cod})(\eta^6\text{-cot})]$ (**6**)^[13] at low temperature by $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ ^[14] in CH_2Cl_2 generates $[\text{Ru}(\text{H})(1,2:5,6-\eta\text{-cod})(\eta^6\text{-cot})](\text{BF}_4)$ (**7**), which rearranges to $[\text{Ru}(\text{H})(1-5-\eta\text{-C}_8\text{H}_{11})_2](\text{BF}_4)$ ($\text{C}_8\text{H}_{11} = 2,4\text{-cyclooctadienyl}$) upon warming. These authors further reported that addition of excess monodentate ligands (H_2O , MeCN, $\text{MeP}(\text{Ph})_2$, ≥ 3 equivalents) to **7** at low temperature followed by warming to ambient temperature produces $[\text{Ru}(1-5-\eta\text{-C}_8\text{H}_{11})(\text{L})_3](\text{BF}_4)$ and 1,3-cyclooctadiene (cod').^[12] We now report that addition of one equivalent of (–)-Me-DuPHOS ((–)-**2**) to **7** in CH_2Cl_2 at -78°C followed by warming to ambient temperature

generates $[\text{Ru}((-)\text{-Me-DuPHOS})(\text{H})(\eta^6\text{-cot})](\text{BF}_4)$ (**1**) in high yield (quantitative by NMR spectroscopy, >80 % yield of isolated product) plus one equivalent of cod [Eq. (3)].



Small amounts (~3 %) of $[\text{Ru}((-)\text{-Me-DuPHOS})(\text{H})(\eta^4\text{-cod})](\text{BF}_4)$ (**8**) also form,^[3] which we identify and discuss below. Addition of more than one equivalent of **(-)-2** leads to the known^[15] $[\text{Ru}((-)\text{-Me-DuPHOS})_2(\text{H})]^+$ by displacement of the cot ligand. Alternatively, **1** can simply be prepared by reaction between **6** and one equivalent of the easily prepared, storable monoprotonated phosphonium salt **(-)-2**·HBF₄^[3] in CH₂Cl₂ at room temperature. The yield of **1** by this procedure is ~88 % (containing ~3 % of **8**). Figure 1 shows the structure

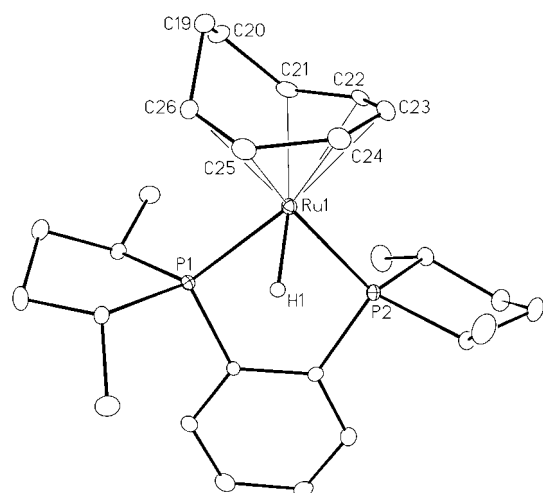
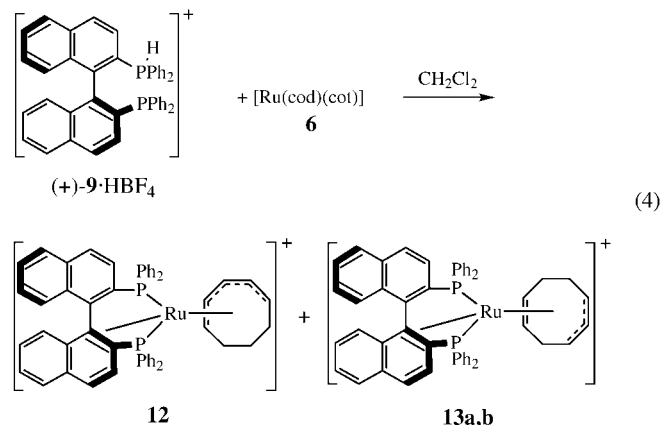


Figure 1. Structure of the cation of **1** in the crystal (all hydrogen atoms except the hydride ligand are omitted for clarity). Selected bond lengths [Å] and angles [°]: Ru–C21 2.380(5), Ru–C22 2.228(4), Ru–C23 2.265(5), Ru–C24 2.226(4), Ru–C25 2.215(5), Ru–C26 2.411(5), Ru–P1 2.305(1), Ru–P2 2.291(1), Ru–H 1.52(4), C19–C20 1.507(8), C20–C21 1.493(7), C21–C22 1.407(7), C22–C23 1.443(7), C23–C24 1.399(6), C24–C25 1.435(7), C25–C26 1.369(7); P1–Ru–P2 84.90(5), P1–Ru–H 68(2), P1–Ru–H 75(2).

of the cation of **1** as determined by X-ray diffraction, which also located the hydride ligand.^[16] The Ru–H bond length (1.52(4) Å) is within the range reported for other Ru–H compounds.^[7, 12, 15, 17] The geometries of the coordinated $\eta^6\text{-cot}$ ^[12, 18] and **(-)-Me-DuPHOS** (**(-)-2**)^[15] ligands compare well to those reported in the literature.

We have adapted this synthesis to incorporate **(+)-BINAP** (**(+)-9**), **(+)-Tol-BINAP** (**(+)-10**),^[5a] and **(-)-JOSIPHOS** (**(-)-11**).^[5d] Reaction of **(+)-9**·HBF₄ with **6** in CH₂Cl₂ at ambient temperature formed a mixture of $[\text{Ru}((+)\text{-BINAP})(1,2,3,4,5\text{-}\eta\text{-C}_8\text{H}_{11})](\text{BF}_4)$ (**12**; ~64 %), and two diastereoisomeric $[\text{Ru}((+)\text{-BINAP})(1,2,3:5,6\text{-}\eta\text{-C}_8\text{H}_{11})](\text{BF}_4)$ (**13a, b**) (~18 % each) [Eq. (4)]. Use of **(+)-10**·HBF₄ gave analogous

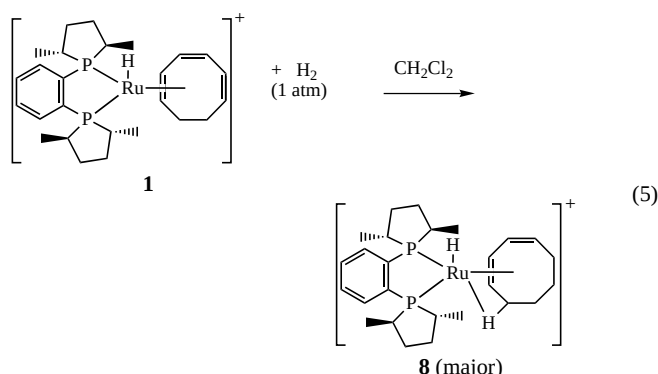


results. Reaction of **7** with **(+)-9** or **(+)-10** at –78°C followed by warming to ambient temperature afforded a mixture consisting of **12** (~82 %) and **13a, b** (~9 % each), or the corresponding Tol-BINAP analogues. The simplest and cleanest procedure is to carry out the protonation of **6** and the subsequent reaction with **(+)-9** at ambient temperature, which yields **12** as the sole product in 86 % yield. Identification of **12** and its Tol-BINAP analogue was accomplished by extensive multinuclear one- and two-dimensional NMR spectroscopy and confirmed by mass spectrometry. In these investigations, we could rely on the prior characterization of two structurally analogous cations, $[\text{Ru}((-)\text{-di-}i\text{Bu-MeOBIPHEP})(1,2,3,4,5\text{-}\eta\text{-C}_8\text{H}_{11})]^+$ and $[\text{Ru}((-)\text{-}i\text{Pr-MeOBIPHEP})(1,2,3,4,5\text{-}\eta\text{-C}_8\text{H}_{11})]^+$ (for which an X-ray crystal structure was provided as well) by Pregosin et al.^[5b,e] In complexes of this type, the P^+P^+ ligands behave as six-electron donors by bonding to Ru through P and through η^2 -coordination to one ring in the binaphthyl or biphenyl backbones.^[5e, 19] Pregosin et al. prepared one of their $[\text{Ru}(\text{P}^+\text{P}^+)(1,2,3,4,5\text{-}\eta\text{-C}_8\text{H}_{11})]^+$ from the same precursor $[\text{Ru}((-)\text{-di-}i\text{Bu-MeOBIPHEP})(\text{OAc})_2]$ as their catalyst $[\text{Ru}((-)\text{-di-}i\text{Bu-MeOBIPHEP})(\text{H})(i\text{PrOH})_2](\text{BF}_4)$ ^[7] (see above), but did not report the use of $[\text{Ru}(\text{P}^+\text{P}^+)(1,2,3,4,5\text{-}\eta\text{-C}_8\text{H}_{11})]^+$ as catalyst precursors. We found that the η^2 -bond to the binaphthyl backbone in **12** is disrupted by excess MeCN to give $[\text{Ru}(\eta^2\text{-}(+)\text{-BINAP})(1,2,3,4,5\text{-}\eta\text{-C}_8\text{H}_{11})(\text{MeCN})](\text{BF}_4)$. Compounds **13a, b** are probably the kinetically formed products and tend to rearrange to the more stable **12**. In the BINAP/Tol-BINAP series, **12** and its analogue are presumably in equilibrium with, but more stable than, the corresponding $[\text{Ru}(\text{P}^+\text{P}^+)(\text{H})(\eta^6\text{-cot})](\text{BF}_4)$, which is favored in the case of Me-DuPHOS.

We found that **(-)-11**·HBF₄ (PCy₂ group protonated) does not react with **6** at room temperature, suggesting that the PCy₂ group is too basic to allow proton transfer to **6**. Our best procedure to produce $[\text{Ru}((-)\text{-JOSIPHOS})(\text{H})(\eta^6\text{-cot})](\text{BF}_4)$

(**14**) is to treat **7** with (–)-**11** in CH₂Cl₂ at –25 °C and then allow the solution to warm to room temperature. This procedure gives a mixture consisting of **14** (one of two possible diastereoisomers; ~85%), plus small amounts of [Ru((–)-JOSIPHOS)(H)(η⁴-cod′)](BF₄) (**15**; ~9%) and of (–)-**11**·HBF₄ (~6%). The ¹H and ¹³C NMR spectra of **14** and **15** are complex. The gross identification of **14**^[20] is based on the diagnostic high-field signal for the hydride ligand in the ¹H NMR spectrum, which correlates with that for **1**, the signals for the η⁶-cot ligand in the ¹³C NMR spectrum, and the mass spectrum. The clean ³¹P NMR spectrum establishes the integrity of the sample. Compound **15** is identified below.

The reaction of **1** with H₂ in CH₂Cl₂ solution at atmospheric pressure and room temperature is rapid, and slows after uptake of about one equivalent of H₂. The major species in solution after the reaction slows is **8** [Eq. (5), one of two

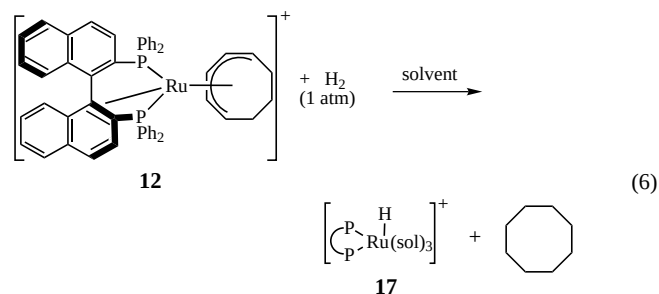


possible diastereoisomers]. The minor species present at this stage are cyclooctane and a number of unidentified Ru hydrides. Compound **8** is formed in near quantitative yield (NMR spectroscopy) when the hydrogenation is carried out at –40 °C. The gross structure of **8** (without assignment of the relative configuration), as determined by multinuclear one- and two-dimensional NMR spectroscopy, has cod′ coordinated to Ru through the double bonds and an allylic agostic C–H interaction. Compound **14** reacts with H₂ in CH₂Cl₂ in an analogous fashion to cleanly give **15**. The identification of **15**^[20] is in part based on the diagnostic high-field ¹H NMR signals for the hydride ligand and the agostic hydrogen atom, which correlate with those for **8**. The identities of **8** and **15** are confirmed by chemical correlation. Excess MeCN entirely displaces the cod′ ligands in **8** and **15** to give the corresponding *fac*-[Ru(P̂P)(H)(MeCN)₃](BF₄) complexes, whose spectral features parallel those of *fac*-[Ru((+)-BINAP)(H)(MeCN)₃](BF₄).^[4a] Compounds **8** and **15** are the minor products from the preparations of **1** and **14** (see above). Their presence is of no consequence when {**1** + **8**} and {**14** + **15**} are used as hydrogenation catalyst precursors because both sets of complexes are fully reduced in donor solvents to give in each case the same catalyst.

In acetone (in which **1** is sparingly soluble: suspension), MeOH, or EtOH, hydrogenation of **1** at atmospheric pressure and room temperature quickly results in the formation of cyclooctane and **5**^[11] (all are soluble in their respective

solvents) in quantitative yield [Eq. (2)]. Solvent exchange is extremely rapid for these complexes. Attempts to isolate them in crystalline form failed; they are only stable in solution and consequently they were identified by NMR spectroscopy. For example, the ¹H, ¹³C, and ³¹P NMR spectra of **5** in [D₆]acetone just show the corresponding signals from the bound ligand (–)-**2**, from the hydride ligand, and from cyclooctane. Brief exposure of **1** to H₂ in the neat substrate **4** under the conditions of the synthesis of (+)-**3**^[3] [Eq. (1), ambient temperature, 90 bar, 5 min, then degassing] results in formation of a *fac*-[Ru((–)-Me-DuPHOS)(H)(**4**)_n](BF₄) (**5**; *n* = 2 or 3), which is apparently a strict analogue of **5**, with **4** as a weakly O-bonded ligand (typical ¹H NMR hydride signal, ³¹P NMR); there is no evidence of alkene coordination to Ru. Hydrogenation of **14** in neat **4** under the same conditions forms in an analogous manner two isomeric [Ru((–)-JOSIPHOS)(H)(**4**)_n](BF₄) (**16**^a, **b**; *n* = 2 or 3). [Ru((–)-JOSIPHOS)(H)(sol)_n](BF₄) **16** apparently reacts further with H₂ in acetone; hydrogenation of **14** in [D₆]acetone at atmospheric pressure and ambient temperature gives a mixture of mainly four hydride species, one of which was identified as **16**. The other three could not be identified with certainty.

Acetone and THF solutions of **12** (with **13**^a, **b** admixed or not) likewise react rapidly under H₂ gas at atmospheric pressure and room temperature to generate in quantitative (NMR) yields *fac*-[Ru((+)-BINAP)(H)(sol)₃](BF₄) (**17**, sol = acetone, THF) and cyclooctane [Eq. (6)]. The magnitude of *J*_{P,H} for all the [Ru(P̂P)(H)(sol)_n](BF₄) reported here and in the literature shows that the hydride ligand always occupies a coordination site mutually *cis* to the phosphorus centers.



In summary, our results outline an apparently versatile synthetic route to the active catalysts [Ru(P̂P)(H)(sol)₃]⁺.^[21] Our catalyst precursors can be prepared easily, in high yield, and they can be stored for long periods at low temperature under argon. A potential limitation of our technique is the synthesis of **6**. The literature yields of this compound vary;^[13] in our hands, the yield was consistently about 35%. Despite this potential limitation, our methodology certainly provides a rapid and effective means for screening [Ru(P̂P)(H)(sol)₃]⁺ catalysts in industrial and academic environments to the degree that [Rh(P̂P)(sol)₂]⁺ catalysts are screened today. Various improvements and variants^[22] can now be envisaged, and the hydrogenation of new, more weakly binding substrates that do not react with conventional Ru^{II} hydrogenation catalysts can now be explored. Our industrial processes in

which the β,γ -unsaturated ester **4**, neat or in very weakly donating solvents such as CH_2Cl_2 , is hydrogenated with our catalysts,^[3] constitute the first examples.

Experimental Section

Operations at ambient temperature were carried out in glove boxes operated with Ar or N_2 , and operations at low temperature were carried out using standard Schlenk techniques and Ar. Operations involving H_2 : operations at atmospheric pressure were carried out by using Schlenk techniques, and operations at 90 bar (all at ambient temperature) in open Teflon or glass tubes placed inside a stainless steel autoclave, which was charged and decharged in a glove box. NMR tubes were sealed under Ar. NMR spectra (^1H at 400.1 MHz, ^{13}C at 100.6 MHz, and ^{31}P at 161.9 MHz) were measured in CD_2Cl_2 at 300 K unless indicated otherwise. H_2 gas (99.99990% and 99.998%) was used as received. All solvents were distilled from appropriate drying agents under Ar.

1 from **6** and (–)-**2**· HBF_4 at ambient temperature: To a stirred solution of **6** (163 mg, 0.517 mmol) in CH_2Cl_2 (5 mL), a solution of (–)-**2**· HBF_4 ^[3] (200 mg, 0.507 mmol) in CH_2Cl_2 (2 mL, another 3 mL was used to rinse) was added dropwise over about 5 min. The solution was stirred for 2 h (color change from amber to red). Slow, dropwise addition of Et_2O (90 mL), filtration, washing with Et_2O (4 × 5 mL) and drying in vacuo afforded **1** as bright yellow microcrystals. Yield 269 mg (0.447 mmol, 88%, containing ca. 3% **8**). NMR spectra in CD_2Cl_2 and MS of **1**: see ref. [3]. In $[\text{D}_6]\text{acetone}/\text{CD}_2\text{Cl}_2$ (1:1, v/v), NMR evidence suggests that an equilibrium mixture (ca. 70/30) of **1** and $[\text{Ru}((\text{–})\text{-Me-DuPHOS})(1,2,3,4,5\text{-}\eta\text{-C}_8\text{H}_{11})(\text{sol})]\text{BF}_4$ **18** is formed within minutes. Spectra for **18**. Partial ^1H NMR: $\delta = 0.38$ (br tq, $J = 13.5$, 2.8 Hz, 1H), 0.60 (dd, $J = 6.7$, 14.3 Hz, 3H), 3.13 (m, 1H), 4.5 (br t, $J = 8.0$ Hz, 1H), 4.95 (m, 1H), 6.93 (br t, $J = 7.0$ Hz, 1H), 7.87, 7.96 (m); $^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta = 70.6$, 84.9 (br.).

12 from **6** and (+)-**9** at ambient temperature: $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ (90 μL , 107 mg, 0.660 mmol) was added dropwise (syringe, ~ 5 min) to a stirred solution of **6** (208 mg, 0.659 mmol) in CH_2Cl_2 (30 mL) (dark brown coloration). After stirring for 2 h, a solution of (+)-**9** (410 mg, 0.658 mmol) in CH_2Cl_2 (10 mL) was added over ~ 5 min while stirring. The resulting solution (maroon) was stirred another 17 h. The solvent was evaporated in vacuo, and the product precipitated as a canary yellow microcrystalline powder by adding Et_2O (100 mL) to a CH_2Cl_2 solution (minimal quantity) of the crude product. The product was washed with Et_2O (2 × 5 mL) and dried in vacuo. Yield 519 mg (0.565 mmol, 86%). ^1H NMR: $\delta = -0.16$ (pseudo-q, $J = 13.5$ Hz, 1H), 0.06 (pseudo-t, $J = 14.0$ Hz, 1H), 0.85 (m, 2H), 1.00 (m, 1H), 1.53 (pseudo-t, $J = 14.0$ Hz, 1H), 1.96, 2.19, 4.63 (m, 1H each), 5.45 (m, 2H), 5.95–8.30 (aromatic); $^{13}\text{C}\{^1\text{H}\}$ NMR: $\delta = 18.9$, 23.2, 27.3 (s, CH_2), 58.5 (t, $J_{\text{PC}} = 3.3$ Hz, CH), 64.1 (d, $J = 35.1$ Hz, aromatic C), 71.6 (d, $J_{\text{PC}} = 19.6$ Hz, CH), 91.0, 96.2 (s, CH), 114.1 (d, $J_{\text{PC}} = 9.5$ Hz, CH), 123–142 (aromatic); $^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta = -5.6$, 64.4 (d, $J_{\text{PP}} = 44.2$ Hz); MS (electrospray ionization): isotopic cluster for $[\text{C}_{52}\text{H}_{43}\text{P}_2\text{Ru}]^+$ centered around 831 m/z .

{14 + 15} from **7** and (–)-**11**: A freshly prepared, cooled (-25°C) solution of $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ (43 μL , 51.3 mg, 0.317 mmol) in CH_2Cl_2 (1 mL) was added dropwise (~ 5 min) to a stirred solution of **6** (100 mg, 0.317 mmol) in CH_2Cl_2 (10 mL) at -25°C (dark amber coloration). After the mixture had been stirred for 20 min at -25°C , a cooled (-25°C) solution of (–)-**11** (1:1 EtOH –adduct, 203 mg, 0.317 mmol) in CH_2Cl_2 (10 mL) was added dropwise (~ 5 min) with stirring. The resulting solution was stirred at -25°C for 2 h, allowed to warm to room temperature, and left at that temperature for 15 h (dark orange solution). The solvent was evaporated in vacuo, and the product precipitated by adding Et_2O (100 mL) to a CH_2Cl_2 solution (minimal quantity) of the crude product. The orange brown product was washed with Et_2O (2 × 5 mL) and dried in vacuo. Yield 215 mg (mixture of **14** (85%), **15** (9%), combined yield 202 mg (0.227 mmol, 72%), and (–)-**11**· HBF_4 (6%)). Hydride ^1H NMR signal for **14**: $\delta = -10.30$ (pseudo-t, $J_{\text{PH}} = 32.5$ Hz, 1H); partial $^{13}\text{C}\{^1\text{H}\}$ NMR: $\delta = 92.9$, 93.1, 94.6, 96.8, (s, CH), 97.7 (br s, CH), 99.1 (s, CH); $^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta = 44.4$, 62.9 (d, $J_{\text{PP}} = 26.2$ Hz); MS (electrospray ionization): isotopic cluster for $[\text{C}_{55}\text{H}_{55}\text{FeP}_2\text{Ru}]^+ - 2\text{H}^+$ centered around 801 m/z . Spectra of **15** (obtained by hydrogenation of **{14 + 15}** in CD_2Cl_2 at -40°C and atmospheric pressure (20 min)). Partial ^1H NMR: $\delta = -19.01$ (pseudo-t, $J_{\text{PH}} = 29.0$ Hz, 1H), -5.20 (br., 1H); $^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta = 65.9$, 43.3 (d, $J_{\text{PP}} = 30.5$ Hz).

Spectra of **8** (obtained by hydrogenation of **1** (+ traces of **8**) in CD_2Cl_2 at -40°C and atmospheric pressure). ^1H NMR (213 K): $\delta = -19.07$ (dd, $J_{\text{PH}} = 34.9$, 24.9 Hz, 1H), -6.53 (br, 1H), 0.55 (dd, $J_{\text{PH}} = 14.9$, $J_{\text{HH}} = 6.7$ Hz, 3H), 0.77 (dd, $J_{\text{PH}} = 15.9$, $J_{\text{HH}} = 6.5$ Hz, 3H), 0.86 (dd, $J_{\text{PH}} = 19.5$, $J_{\text{HH}} = 6.8$ Hz, 3H), 0.98 (m, 1H), 1.29 (dd, $J_{\text{PH}} = 19.1$, $J_{\text{HH}} = 6.9$ Hz, 3H, overlapping with signal for 1H), 1.48 (m, 2H), 1.55–1.78 (m, 4H), 1.84 (m, 3H), 2.05, 2.15 (m, 1H each), 2.24–2.53 (m, 4H), 2.59, 2.68, 4.50, 5.13, 5.28, 6.37 (m, 1H each), 7.40–7.90 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (213 K): $\delta = 11.3$ (s, CH_2), 13.1, 13.8 (s, CH_3), 17.9 (d, $J_{\text{PC}} = 8.8$ Hz, CH_3), 18.8, 19.6 (s, CH_2), 19.7 (d, $J_{\text{PC}} = 8.8$ Hz, CH_3), 27.2 (s, CH_2), 34.0 (d, $J_{\text{PC}} = 25.2$ Hz, CH), 35.2, 35.9 (s, CH_2), 36.2 (d, $J_{\text{PC}} = 5.6$ Hz, CH_2), 36.7 (s, CH_2), 39.5 (d, $J_{\text{PC}} = 27.2$ Hz, CH), 39.7 (d, $J_{\text{PC}} = 31.9$ Hz, CH), 44.2 (d, $J_{\text{PC}} = 35.0$ Hz, CH), 78.8 (d, $J_{\text{PC}} = 13.3$ Hz, CH), 79.6, 92.1, 102.4, 130.7, 130.9 (s, CH), 131.3 (d, $J_{\text{PC}} = 13.6$ Hz, CH), 132.3 (d, $J_{\text{PC}} = 13.6$ Hz, CH), 142.2 (d, $J_{\text{PC}} = 38.0$ Hz, aromatic C), 142.7 (dd, $J_{\text{PC}} = 32.0$, 8.9 Hz, aromatic C); $^{31}\text{P}\{^1\text{H}\}$ NMR (213 K): $\delta = 87.2$, 92.2 (d, $J_{\text{PP}} = 17.3$ Hz).

Spectra of **5** (obtained by hydrogenation of **1** (+ traces of **8**) in $[\text{D}_6]\text{acetone}$ at room temperature and atmospheric pressure (20 min)). ^1H NMR: $\delta = -22.29$ (pseudo-t, $J = 34.5$ Hz, 1H), 0.64 (dd, $J_{\text{PH}} = 14.4$, $J_{\text{HH}} = 7.1$ Hz, 3H), 0.83 (dd, $J_{\text{PH}} = 13.2$, $J_{\text{HH}} = 7.2$ Hz, 3H), 1.08 (dd, $J_{\text{PH}} = 16.0$, $J_{\text{HH}} = 7.2$ Hz, 3H), 1.19 (dd, $J_{\text{PH}} = 16.0$, $J_{\text{HH}} = 7.2$ Hz, 3H), 1.32, 1.78 (m, 2H each), 2.00–2.30 (m, 6H), 2.61, 7.49, 7.78 (m, 2H each); $^{13}\text{C}\{^1\text{H}\}$ NMR: $\delta = 12.7$, 15.0 (s, CH_3), 17.6 (d, $J_{\text{PC}} = 9.1$ Hz, CH_3), 18.6 (d, $J_{\text{PC}} = 7.6$ Hz, CH_3), 35.7, 36.4 (s, CH_2), 36.5 (d, $J_{\text{PC}} = 6.1$ Hz, CH_2), 37.1 (d, $J_{\text{PC}} = 4.6$ Hz, CH_2), 37.6 (d, $J_{\text{PC}} = 22.9$ Hz, CH), 38.3 (d, $J_{\text{PC}} = 22.9$ Hz, CH), 43.1 (d, $J_{\text{PC}} = 33.6$ Hz, CH), 129.6 (d, $J_{\text{PC}} = 16.8$ Hz, CH), 129.9 (dd, $J_{\text{PC}} = 16.8$, 2.7 Hz, CH), 130.5 (d, $J_{\text{PC}} = 15.3$ Hz, CH), 130.6 (d, $J_{\text{PC}} = 13.7$ Hz, CH); $^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta = 113.9$, 118.3 (d, $J_{\text{PP}} = 34.9$ Hz).

Spectra of **5'** in neat **4** (obtained by hydrogenation of **1** in **4** at room temperature and 90 bar (5 min) and degassing). Hydride ^1H NMR signal: $\delta = -21.81$ (br t, $J_{\text{PH}} \sim 34.5$ Hz); $^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta = 113.9$, 115.6 (br d, $J_{\text{PP}} \sim 33$ Hz).

Spectra of **16'a,b** in neat **4** (obtained by hydrogenation of **{14 + 15}** in **4** at room temperature and 90 bar (5 min) and degassing). Hydride ^1H NMR signals: major species $\delta = -28.62$ (br t, $J_{\text{PH}} \sim 33$ Hz), minor $\delta = -23.00$ (br.); $^{31}\text{P}\{^1\text{H}\}$ NMR: major $\delta = 70.5$, 90.8 (d, $J_{\text{PP}} = 45.8$ Hz), minor $\delta = 60.6$, 93.0 (br d, $J_{\text{PP}} \sim 53$ Hz).

Spectra of **17** (obtained by hydrogenation of **12** in $[\text{D}_6]\text{acetone}$ at room temperature and atmospheric pressure (20 min)). ^1H NMR: $\delta = -19.80$ (pseudo-t, $J = 30.8$ Hz, 1H), 6.3–8.0 (aromatic); $^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta = 71.2$, 79.7 (d, $J_{\text{PP}} = 49.4$ Hz).

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A New Photomagnetic Molecular System Based on Photoinduced Self-Assembly of Radicals**

Imma Ratera, Daniel Ruiz-Molina, José Vidal-Gancedo, Klaus Wurst, Nathalie Daro, Jean-François Létard, Concepció Rovira, and Jaume Veciana*

Dedicated to Professor Fred Wudl
on the occasion of his 60th birthday

The synthesis and characterization of supramolecular magnetic materials based on the self-assembly of open-shell molecules are currently of great interest.^[1] The construction of such solids requires that the structural subunits exhibit noncovalent interactions that can be controlled in a predictable manner. The noncovalent intermolecular interactions that have been used to date for the assembly of such molecular subunits are hydrogen bonding,^[2] transition metal

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ligation,^[3] stack-type alignment,^[4] and bridging of ion radicals by their counterions.^[5] Among these interactions, hydrogen bonding has emerged as a particularly useful and efficient tool. Indeed, transmission of magnetic interactions through hydrogen bonds was first observed with transition metal complexes.^[6] Since then, several hydrogen-bonded organic magnets have been reported.^[2] However, to the best of our knowledge, hydrogen-bonded supramolecular magnetic materials whose properties may be systematically tuned and/or controlled by external stimuli have so far not been reported despite the enormous interest in switchable magnetic materials.

Light is a particularly efficient stimulus for inducing changes in the magnetic properties of a given material. In fact, examples of photomagnetism in inorganic magnetic systems and in covalently linked organic polyradicals have already been reported. For instance, Hashimoto et al. reported photoinduced magnetization changes in a cobalt–iron cyanide complex,^[7] which confirmed the possibility of modifying long-range magnetic ordering by photons. Furthermore, photoinduced magnetic changes in pure organic materials have also been described, for example, as in the photoisomerization of a carbene^[8] and in the spin isomerism of a non-Kekulé diradical.^[9] More recently, Irie and Matsuda described a photochromic system that interconverts reversibly between a singlet and a triplet high-spin ground state,^[10] and Iwamura et al. reported a diradical species bearing two stable nitroxide radicals connected through an isomerizable unit.^[11]

Herein we report a new photomagnetic system based on the photoinduced *trans*→*cis* isomerization of **1**. The *trans*-**1** isomer exists in solution as a monomeric species, whereas the *cis*-**1** isomer aggregates in solution through the formation of hydrogen bonds to give a thermodynamically stabilized diradical dimer with strong antiferromagnetic interactions. Although numerous photochromic supramolecular systems have been described up to now,^[12] this photoinduced self-assembly process represents the first example of a photomagnetic system based on a supramolecular phenomenon.

The ferrocenyl Schiff base polychlorotriphenylmethyl radical (**1**) was obtained by a condensation reaction between the (4-amino-2,6-dichlorophenyl)bis(2,4,6-trichlorophenyl)methyl radical and ferrocene monocarboxaldehyde. Since the condensation reaction is not stereoselective, the *trans* and *cis* isomers of compound **1** were present in the reaction product. Both isomers, *trans*-**1** and *cis*-**1**, were isolated as stable species in solution and in the solid state, and were characterized by different techniques such as elemental analysis, matrix-assisted laser desorption time-of-flight (MALDI-TOF) mass spectrometry, HPLC, cyclic voltammetry, FT-IR, UV/Vis/NIR, and ESR spectroscopy.

Single crystals for the X-ray structure analysis of *trans*-**1** were grown by slow evaporation from a carbon tetrachloride/hexanes (1/1) mixture.^[13] The structure of *trans*-**1** (Figure 1; ORTEP view) reveals almost eclipsed cyclopentadienyl rings and a *trans* configuration at the CH=N double bond. Despite the available resonance pathway and the *trans* configuration, the η -C₅H₄ and the C₆H₂Cl₂ rings are twisted by an angle of about 28°. Presumably, the steric interactions between the hydrogen atom of the CH=N group and one of the *ortho* hydrogen

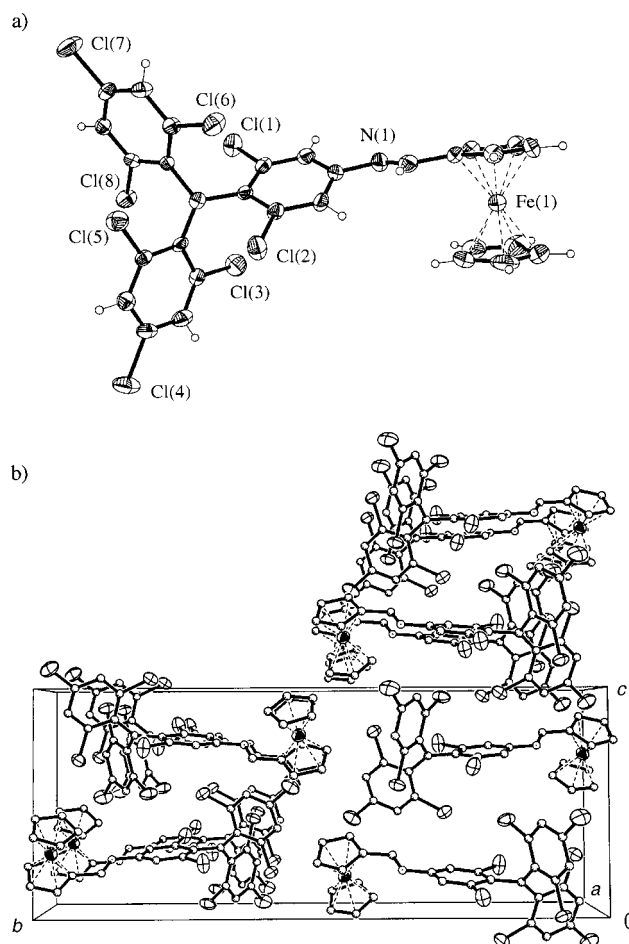
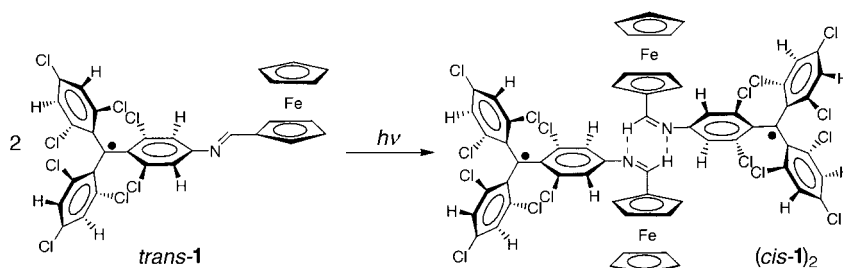


Figure 1. Molecular structure (with 50% ellipsoids; top) and crystal packing (bottom) of *trans*-**1**.

atoms of the benzene ring prevents a planar arrangement. The solid-state packing of *trans*-**1** is best described as enantiomerically related pairs of molecules (see Figure 1b). Stacking of these related pairs occurs with continuous staggering along the *c* axis and with a head-to-tail pairing along the *b* axis. The relative arrangement and the considerably large distances between neighboring molecules excludes the presence of hydrogen bonds among neighboring CH=N units. Under these circumstances, the largest driving forces for such molecular packing are dipole–dipole and van der Waals interactions, which lead to an efficient filling of space. Unfortunately, despite the use of different crystallization techniques, we have been unable to obtain crystals suitable for determining the X-ray structure of the *cis*-**1** isomer.^[14]

The cyclic voltammetric response of *trans*-**1** and *cis*-**1** show one reversible oxidation process at +0.61 and +0.72 V, respectively, and one reversible reduction process at –0.66 and –0.67 V, respectively (vs. a Ag/AgCl electrode in CH₂Cl₂). The reversible oxidation process arises, in both cases, from the oxidation of the iron atom of the ferrocene unit, while the reversible reduction process is associated with the reduction at the triphenylmethyl radical unit to the corresponding carbanion; as ascertained by UV/Vis and ESR spectroelectrochemical experiments. ESR spectroscopy provides more detailed and definitive information about the

molecular and electronic structure of both isomers in solution. Thus, the isotropic X-band ESR spectrum of the radical *trans*-**1** in toluene/dichloromethane (1/1; $c = 10^{-5} \text{ mol L}^{-1}$) at 220 K, is concentration-independent and shows the lines corresponding to the coupling of the unpaired electron with the different nuclei with nonzero magnetic moments; that is, with ^1H , ^{14}N , and naturally abundant ^{13}C isotopes at the α and aromatic positions. Computer simulation gave the isotropic g values (g_{iso}) and the isotropic hyperfine coupling constants (a_i). The g_{iso} value is 2.0030, which is very close to the values for other polychlorotriphenylmethyl radicals.^[15] The values of the coupling constants of *trans*-**1** are: $a(^{14}\text{N}) = 1.18 \text{ G}$; $a(^1\text{H}_{\text{meta}}) = 1.06 \text{ G}$; $a(^1\text{H}_{\text{trans}}) = 0.25 \text{ G}$; $a(^{13}\text{C}_{\alpha}) = 28.5 \text{ G}$; $a(^{13}\text{C}_{\text{bridge}}) = 12.5 \text{ G}$; $a(^{13}\text{C}_{\text{ortho}}) = 10.3 \text{ G}$.^[16] At 160 K, its spectrum shows a single broad line characteristic of an isolated free radical in a rigid medium with a low magnetic anisotropy. This fact clearly shows that the *trans*-**1** isomer exists in solution as a monomeric species. Surprisingly, the X-band ESR spectrum of the *cis*-**1** radical in toluene/dichloromethane (1/1) at 220 K did not show the lines corresponding to the coupling of the unpaired electron with the different magnetic nuclei, but the characteristic fine structure of a triplet species. The zero-field splitting parameters obtained by computer simulation of the spectra obtained at 160 K are $|D'| = 25.2 \text{ G}$ and $|E'| = 0$. This behavior has been attributed to the formation of a dimeric species which is held together by intermolecular C-H...N hydrogen bonds between the CH=N groups of two different molecules (Scheme 1). Semiempirical ZINDO/1 calculations^[17] revealed that the H-bonded dimeric form of *cis*-**1** corresponds to an energy minimum, while for the *trans*-**1** isomer similar H-bonded dimeric or polymeric species



Scheme 1. Photoinduced *trans* $\rightarrow$ *cis* isomerization of **1**.

do not correspond to energy minima; probably because of the steric hindrance developed in such species. These calculations also revealed that the dimeric species (*cis*-**1**)₂ are more stable than the monomeric species *trans*-**1** by 7 kcal mol⁻¹. The forbidden $\Delta m_s = \pm 2$ transition characteristic of triplet species was also observed at the half-field region of the spectrum of *cis*-**1** and the intensity of the corresponding signal (I_{pp}), obtained by double integration, was measured in the 4–100 K temperature range. Since the experimental value of $I_{\text{pp}}T$ is proportional to the population in the triplet state, the fact that $I_{\text{pp}}T$ decreases with decreasing temperature indicates that the ground state of the dimeric species is the singlet state and the triplet state should be associated with a thermally accessible excited state. A separation of $54 \pm 2 \text{ K}$ (38 cm^{-1}) between

both states was obtained from the fitting of the experimental data to a Bleaney–Bowers equation.^[18]

Our interest in compound **1** was considerably enhanced when it was found that the ESR spectrum of *trans*-**1** in methylcyclohexane exhibited a time dependence behavior under in situ irradiation at 415 nm,^[19] a result that is consistent with the conversion from the *trans*-**1** to the *cis*-**1** isomer (Figure 2). After eight hours of irradiation a mixture with a

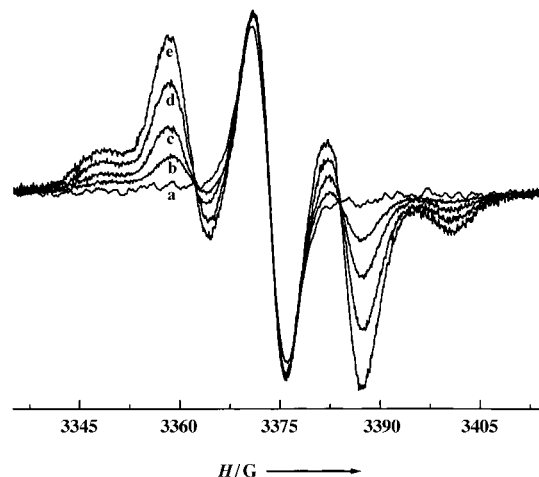
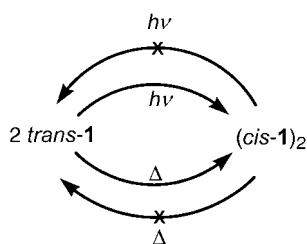


Figure 2. Photoinduced *trans* $\rightarrow$ *cis* isomerization of **1** monitored by ESR spectroscopy. $t = 0$ (a), 1 (b), 3 (c), 5 (d), 8 h (e).

cis:trans ratio $\geq 90:10$ was obtained; as confirmed by computer simulation. The photoinduced *trans*-**1** $\rightarrow$ *cis*-**1** isomerization in methylcyclohexane at room temperature was also monitored by UV/Vis spectroscopy. Indeed, the *trans*-**1** and

cis-**1** isomers show characteristic UV/Vis absorption bands for the radical (377 nm) and conjugated ferrocene (408 nm) chromophores. The main difference lies in the relative intensity of both bands. The band at 377 nm for the *trans*-**1** isomer is less pronounced, whereas that at 408 nm is more intense than the corresponding bands for the *cis*-**1** isomer. This fact allowed us to study the effect of irradiation upon a solution of *trans*-**1** in methylcyclohexane by UV/Vis spectroscopy. The in situ irradiation of *trans*-**1** ($c = 10^{-5} \text{ mol L}^{-1}$ in methylcyclohexane) was carried out using 415 nm

light in a quartz cell at room temperature for 2 h. During the irradiation of the *trans*-**1** solution, the absorption band at 377 nm increases, whereas the absorption band at 408 nm decreases; an isosbestic point occurs at 382 nm. This confirms a neat transformation from the *trans*-**1** to the *cis*-**1** isomer. Finally, it must be emphasized that irradiation of a *cis*-**1** solution ($c = 10^{-5} \text{ mol L}^{-1}$) did not indicate the presence of the reverse photoisomerization process, either by ESR and/or by UV/Vis spectroscopy. Moreover, warming *cis*-**1** solutions in three different solvents (methylcyclohexane, toluene, and acetonitrile) up to 80 °C provided no evidence of a thermally induced backward *cis*-**1** $\rightarrow$ *trans*-**1** isomerization, while the *trans*-**1** $\rightarrow$ *cis*-**1** isomerization process takes place in the three studied solvents (Scheme 2).



Scheme 2. Overview of the photochemically and thermally possible isomerizations of **1**.

In summary, the photoinduced *trans* → *cis* isomerization of **1** has been monitored by UV/Vis and ESR spectroscopy. Interestingly, the *cis*-**1** isomer aggregates in solution at low temperatures through the formation of hydrogen bonds to give thermodynamically stable diradical dimers with strong antiferromagnetic interactions. This

one-way photoinduced self-assembly process represents an interesting example of a photomagnetic system based on a supramolecular phenomenon in which a doublet species is converted into a singlet one.

Experimental Section

1: To a dry solution of (4-amino-2,6-dichlorophenyl)bis(2,4,6-trichlorophenyl)methyl radical in toluene, which was obtained as previously described,^[20] was added ferrocene monocarboxaldehyde in the presence of molecular sieves. The mixture was heated up to 60 °C and stirred for 48 h. After removal of the molecular sieves and evaporation of the solvent, a brown precipitate was obtained, which contained a mixture of *cis*- and *trans*-**1**. The *trans*-**1** isomer was isolated as a dark brown microcrystalline material by recrystallization from *n*-hexane, and the *cis*-**1** isomer was isolated as a dark green powder by flash chromatography (Florisil (magnesium silicate), carbon tetrachloride). *trans*-**1**: elemental analysis (%): calcd for C₃₀H₁₆Cl₈NFe: C 49.4, H 2.21, N 1.90; found: C 49.6, H 1.8, N 2.1; IR (KBr): $\tilde{\nu}_{\text{max}}$ = 3420, 2967, 2913, 1631, 1556, 1536, 1465, 1371, 1261, 1225, 1182, 1137, 1104, 1021, 858, 809 cm⁻¹; UV/Vis (methylcyclohexane): $\lambda(\epsilon)$ = 377 (20300), 409 (14900), 565 nm (1863). *cis*-**1**: elemental analysis (%): calcd for C₃₀H₁₆Cl₈NFe: C 49.4, H 2.21, N 1.90; found: C 49.8, H 2.0, N 2.2; IR (KBr): $\tilde{\nu}_{\text{max}}$ = 3434, 2925, 2849, 1715, 1631, 1552, 1526, 1487, 1383, 1371, 1292, 1227, 1182, 1134, 1076, 1057, 926, 858, 817, 788 cm⁻¹; UV/Vis (methylcyclohexane): $\lambda(\epsilon)$ = 377 (23300), 407 (13600), 578 nm (2940).

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Fluoroprolines as Tools for Protein Design and Engineering**

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Nediljko Budisa, Robert Huber, and Luis Moroder*

The naturally occurring fluorine isotope, ^{19}F , has excellent nuclear magnetic resonance properties.^[1] It is the second most sensitive nucleus after hydrogen and exhibits even higher sensitivity towards changes in its chemical environment. Despite some minor differences in the van der Waals radius and particularly in length and dipole moment of the C–F bond, fluorine is generally considered as isosteric to hydrogen that it replaces. Taking into account that fluorine occurrence in biological molecules is extremely rare,^[2] natural background signals are absent, and thus ^{19}F NMR spectroscopy has become a useful tool for investigating protein structure and dynamics, as well as interactions between fluorinated ligands and receptors. In vivo incorporation of (4S)-fluoroproline ((4S)-FPro) into collagen and its proto- and procollagen precursors has been observed in cell cultures; its effect was to decrease the stability and/or folding rate of the collagen triple helix.^[3] Conversely, in synthetic collagen model peptides that contain (4R)-4-fluoroproline at the positions of hydroxyproline, the stability of the triple helical fold was found to be markedly enhanced,^[4] a fact which was attributed to the inductive effect of fluorine as derived from the kinetic and thermodynamic properties of (4R)-FPro in dioxane.^[5]

For a more appropriate correlation between the thermodynamics of the *cis/trans* isomerization of fluorinated prolines and the stability of related protein mutants, we have characterized in a comparative study the kinetics and thermodynamics of the isomerization of Ac-L-Pro-OMe (**1**), Ac-(4R)-L-FPro-OMe (**2**), Ac-(4S)-L-FPro-OMe (**3**), and Ac-(4)-L-F₂Pro-OMe (**4**) in aqueous solution by FT-IR and $^1\text{H}/^{19}\text{F}$ NMR spectroscopy. The observed preference of Ac-(4S)-L-FPro-OMe for the *cis* conformation compared to the situation for **1** and particularly to that for **2** was confirmed by the differentiated thermostabilities of related barstar mutants.

In the model compounds the known pH effect on the isomerization of Xaa-Pro bonds^[6] was prevented by the N- and C-derivatization. The inductive effect of the F substituents, reported previously for Ac-(4R)-L-FPro-OMe (**2**) in dioxane,^[5] was observed in aqueous media for both monofluorinated proline derivatives **2** and **3**, and as expected, more intensively for the difluoro derivative **4** by a blue shift of the amide–I band (C=O stretching) compared to that of **1** in the FT-IR spectrum (**2**: +8.5 cm^{−1}, **3**: +12.5 cm^{−1}, **4**: +18 cm^{−1}). This strengthening of the C=O bond accompanies a weakening of the double-bond character of the Ac-Pro amide bond. This inductive effect is also well evidenced by the pK_a value of the immonium group of the free amino acid L-4,4-F₂Pro (7.15 ± 0.1) compared to the known pK_a values of 9.2 for (4R)-L-FPro and of 10.8 for L-Pro.^[5] The resulting pyramidization of the N atom of the Ac-Pro bond leads to an acceleration of the *trans/cis* isomerization in the order **1** < **2** < **3** < **4** (Figure 1). From Eyring plots of the isomerization rates

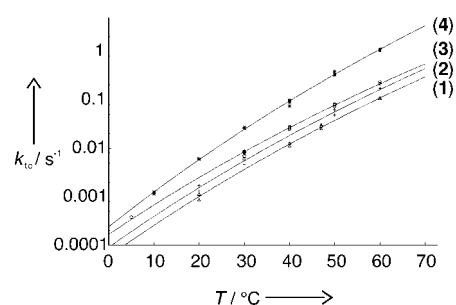


Figure 1. Logarithmic plot of the *trans* → *cis* isomerization rates k_{ic} of compounds **1**–**4** versus temperature. This type of plot is similar, but not equivalent to an Eyring plot; it was used to allow direct extraction of the isomerization rates k_{ic} . Multiple symbols at one temperature indicate multiple measurements with different NOESY mixing times (τ_m).

k_{ic} between 4 and 60 °C the activation enthalpy $\Delta H^\ddagger$ and entropy $\Delta S^\ddagger$ were determined (Table 1). The equilibrium constants K_{ZE} (*trans/cis* isomer ratios) show a completely different behavior, that is an order of **3** < **4** < **1** < **2** (Figure 2).

Table 1. Activation enthalpy ($\Delta H^\ddagger$) and entropy ($\Delta S^\ddagger$) as derived from Eyring plots. Error limits obtained from the residuals of the linear least-squares fitting were 1–2 % for compounds **1**, **3**, and **4**, and 2–3 % for compound **2**. Additionally the free energy of activation at 300 K ($\Delta G_{300\text{K}}^\ddagger$) is given.

Proline derivative	<i>trans</i> → <i>cis</i>			<i>cis</i> → <i>trans</i>		
	$\Delta H^\ddagger$ [kJ mol ^{−1}]	$\Delta S^\ddagger$ [J mol ^{−1} K ^{−1}]	$\Delta G_{300\text{K}}^\ddagger$ [kJ mol ^{−1}]	$\Delta H^\ddagger$ [kJ mol ^{−1}]	$\Delta S^\ddagger$ [J mol ^{−1} K ^{−1}]	$\Delta G_{300\text{K}}^\ddagger$ [kJ mol ^{−1}]
Ac-Pro-OMe 1	92.3	12.8	88.4	87.2	9.00	84.5
Ac-(4R)-FPro-OMe 2	91.8	14.8	87.4	84.2	5.37	82.6
Ac-(4S)-FPro-OMe 3	87.5	4.17	86.3	84.7	2.42	84.0
Ac-4,4-F ₂ Pro-OMe 4	103.7	66.38	83.8	98.5	59.11	80.8

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Unexpectedly, the free energy difference between the *cis* and *trans* isomer is smallest for the (4S)-L-FPro derivative **3** (Table 2), while the K_{ZE} value for the difluoro derivative **4** is somewhat smaller than that of the proline compound **1**. van't Hoff plots served to derive the enthalpic and entropic contributions to the free energy difference between the *cis* and *trans* isomers (Table 2); these contributions are in good agreement with the corresponding differences between $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for the *cis* → *trans* and the *trans* → *cis* isomerization.

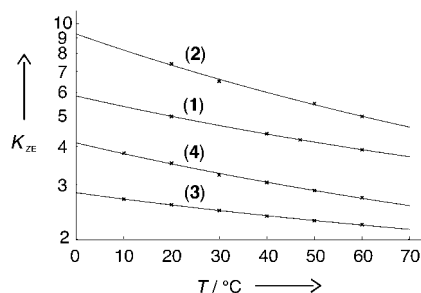


Figure 2. Logarithmic plot of the equilibrium constants K_{ZE} of the *trans/cis* isomerization of the amide bond of compounds **1–4** versus temperature. This type of plot is similar, but not equivalent to a van't Hoff plot; it was used to allow direct extraction of the K_{ZE} values.

Table 2. Enthalpy (ΔH^0) and entropy (ΔS^0) contributions to free energy difference between *trans* and *cis* isomers as derived from van't Hoff plots. Error limits were obtained from the residuals of the linear least-squares fitting. Additionally the free energy difference ΔG^0 at 300 K is given.

Proline derivative	ΔH^0 [kJ mol ⁻¹]	ΔS^0 [J mol ⁻¹ K ⁻¹]	$\Delta G^0_{300\text{ K}}$ [kJ mol ⁻¹]
Ac-Pro-OMe 1	−5.04 (±1.0 %)	−3.82 (±4.3 %)	−3.90
Ac-(4 <i>R</i>)-FPro-OMe 2	−7.73 (±3.3 %)	−9.81 (±8.3 %)	−4.78
Ac-(4 <i>S</i>)-FPro-OMe 3	−3.04 (±1.1 %)	−2.47 (±4.3 %)	−2.30
Ac-4,4-F ₂ Pro-OMe 4	−5.21 (±2.3 %)	−7.32 (±5.3 %)	−3.01

The large difference in the K_{ZE} values of **2** and **3** relates to the different pucker of the proline ring. For 4-fluoro-L-proline the influence of the substitution site (*S* or *R*) on the proline ring pucker was determined as early as 1973 by NMR spectroscopy.^[7] From ¹H–¹H and ¹H–¹⁹F NMR coupling constants a γ -*exo*-puckered structure was derived for (4*R*)-L-FPro and a γ -*endo*-puckered structure for (4*S*)-L-FPro, both as free amino acids. By analyzing the acetyl methyl ester derivatives **1–4** in the present study, the ¹H–¹H and ¹H–¹⁹F coupling patterns were indicative of a γ -*endo*-puckered structure for all compounds except for Ac-(4*R*)-L-Pro-OMe (**2**) which exhibits a γ -*exo*-pucker, and this independently of the *trans* or *cis* conformation of the Ac-Pro amide bond. The crystal structures of (4*R*)-L-Pro and L-Pro as free amino acids exhibit the same pucker as determined by NMR analysis, that is a γ -*exo*-pucker for (4*R*)-L-FPro and a γ -*endo*-pucker for Pro.^[8] The γ -*exo*-pucker of the proline ring for (4*R*)-L-FPro and the γ -*endo*-pucker for (4*S*)-L-FPro is explained by the *gauche* effect.^[4] For the difluoro derivative the *gauche* effects of both fluorine atoms counteract leading to behavior more similar to that of proline, namely a preference for the *endo*-pucker. Molecular modeling experiments show that due to steric hindrance, the energy difference between the *cis* and *trans* isomer is significantly larger for the *exo*-pucker than for the *endo*-pucker. This would suggest that a preference for the *endo*-pucker leads to a smaller energy difference between the *cis* and *trans* isomers and, therefore, to a larger population of the *cis* isomer state at equilibrium as indeed experimentally observed for (4*S*)-L-FPro in comparison to (4*R*)-L-FPro. These results fully agree with a recent Brookhaven data base analysis of peptide bonds in proteins^[9] which showed that *cis* Xaa-Pro bonds are accompanied by an *endo*-pucker of the proline, whereas for *trans* Xaa-Pro bonds no preferred pucker was observed.

To correlate the thermodynamic data derived from the model compounds with the thermostability of 4-FPro-mutants of proteins, as a model protein we have chosen barstar, a single-domain extracellular RNase inhibitor protein which contains two proline residues, that is Pro27 in the *trans* and Pro48 in the *cis* conformation. For the substitution experiments the barstar mutant b*C40A/C82A/P27A was used which lacks complications arising from oxidation of cysteine residues in the wild-type form and from isomerization affecting the peptidyl-Pro27 bond. This triple mutant protein contains only one proline residue (Pro48) being in *cis* conformation in the native state, located in a loop region almost completely exposed to the solvent.^[10] The fluorinated prolines (4*R*)-L-FPro and (4*S*)-L-FPro were incorporated into the barstar (b*C40A/C82A/P27A) at the sequence position Pro48 in a response to a CCG codon-containing DNA-template (plasmid) during fermentation with the proline-auxotrophic *E. coli* host strain DSM 1562 under efficient selective pressure;^[11, 12] to our knowledge this is the first incorporation of fluorinated prolines into proteins through a bacterial expression system. The yields of mutants were comparable to those of the nonfluorinated barstar mutant (Figure 3). As expected, the (4*S*)-L-FPro mutant showed a higher thermostability (T_m = 69.4 °C) and the (4*R*)-L-FPro mutant a lower stability (T_m = 61.5 °C) than barstar b*C40A/C82A/P27A (T_m = 64.3 °C). In preliminary experiments difluoroproline was also incorporated into barstar, but without marked change in stability (T_m = 64.2 °C); the detailed biophysical characterization of all barstar mutants will be reported elsewhere.

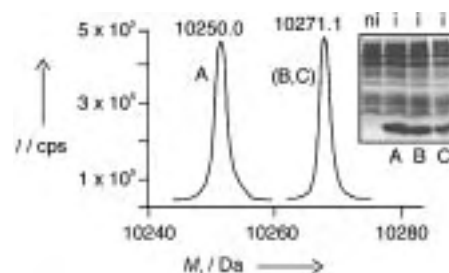


Figure 3. Left: Deconvoluted ESI-MS spectra of two separate measurements of barstar b*C40A/C82A/P27A (**A**; M_r = 10250 Da) and of the related P48(4*R*)-L-FPro (**B**) and P48(4*S*)-L-FPro (**C**) mutants, M_r = 10271 Da. Right: Expression profile of barstar b*C40A/C82A/P27A and its FPro-mutants: ni = noninduced cells (control); i = induced cells.

The successful expression of the barstar mutants confirms that fluorinated prolines are recognized by their cognate aminoacyl-tRNA synthetases and are incorporated into proteins as efficiently as fluorinated tyrosines,^[13] tryptophans,^[14] and phenylalanines.^[15] Moreover, depending upon the (4*S*)- or (4*R*)-FPro isomer used, the *cis* or *trans* conformation of peptidyl-Pro bonds can be favored and disfavored, respectively, relative to proline itself, even in proteins. Conversely, bioincorporation of the difluoroproline into proteins is expected to yield mutants with unchanged thermostabilities, but bearing the valuable fluorine label for NMR structural analysis. The modulation of protein properties by synthetic amino acids with a priori defined properties,

as demonstrated here, opens a rather new avenue to the rational design and engineering of proteins.

Experimental Section

The compounds Ac-(4*R*)-L-FPro-OMe (**2**), Ac-(4*S*)-L-FPro-OMe (**3**), and Ac-(4)-L-F₂Pro-OMe (**4**) were prepared according to the method developed by Demange et al.,^[16] and Ac-Pro-OMe (**1**) by standard procedures. FT-IR spectra were recorded at 25 °C on a Perkin-Elmer 1760 X FT-IR spectrometer using an ATR cell (ATR = attenuated total reflection). For thermal unfolding experiments a JASCO J-715 spectropolarimeter equipped with a Peltier-type FDCD attachment, model PFD-350S/350L was employed and samples were measured in rectangular 110-QS Hellma quartz cells with an optical path length of 0.1 cm. The melting curves of wild-type as well as substituted proteins were acquired in the range 25–95 °C in 50 mM sodium dihydrogen phosphate with 20 mM Tris/HCl buffer (Tris = tris(hydroxymethyl)aminomethane) at pH 8.0. The unfolding profile was recorded at 222 nm at a protein concentration of 0.2 mg mL⁻¹ using a temperature gradient of 50 °C h⁻¹ as described elsewhere. Samples for NMR measurements were prepared by dissolving the compounds (3 mg) in D₂O (0.5 mL). All NMR experiments were performed on a Bruker DRX500 spectrometer using either a triple-resonance (¹⁵N/¹³C/¹H) inverse or a dual (¹⁹F/¹H) inverse probe. ¹H, ¹³C, and ¹⁹F NMR signals were assigned based on homonuclear 2D ¹H–¹H NOESY and TOCSY experiments and heteronuclear 2D ¹⁹F–¹H and ¹³C–¹H COSY experiments.^[17]

Thermodynamics and kinetics of amide bond isomerization: Equilibrium constants (*K*_{ZE}) for the *trans*/*cis* isomer ratios at various temperatures were determined by integration of signals in the 1D-¹H and 1D-¹³C NMR spectrum for compounds **1–3**, and in the 1D-¹⁹F NMR spectrum for **4**. For the 4-FPro derivatives ¹⁹F NMR signals of the *cis* and *trans* isomer overlapped to such an extent that neither determination of the equilibrium constants nor measurement of the isomerization rates was possible by ¹⁹F NMR spectroscopy. Comparison of *K*_{ZE} values obtained from 1D-¹H and 1D-¹³C NMR spectra revealed that resonances from γ and δ protons were the most suitable for integration. The enthalpic and entropic contributions to the free energy difference between the *cis* and *trans* isomers were obtained from van't Hoff plots according to $\ln(K_{ZE}) = (-\Delta H^0/R)(1/T) + \Delta S^0/R$. The rate constants *k*_{EZ} for the *cis*→*trans* and *k*_{ZE} for *trans*→*cis* isomerization of the Ac-Pro amide bond were determined from 2D NOESY spectra. For the (4)-F₂Pro derivative **4** cross peaks between ¹⁹F_{γ^{trans}} and ¹⁹F_{γ^{cis}} in the ¹⁹F–¹⁹F NOESY spectrum were integrated and compared to integrals of the corresponding diagonal signals. To avoid the influence of differential *T*₁ times, only cross and diagonal peaks with the same *F*₁ frequency (indirect) and not with the same *F*₂ (direct) frequency were compared. For compounds **1–3** cross peaks between ¹H_{α^{trans}} and ¹H_{α^{cis}} in the ¹H–¹H NOESY spectrum were used since only these were separated well enough in the spectra. The cross peak to diagonal peak ratios thus obtained were scaled as follows to account for differential relaxation behavior of the

resonances:^[18] $k_{EZ} = (I_{ct}/I_{cc} + (I_{ct}/I_{tt})K_{ZE})/(2\tau_m)$, $k_{ZE} = ((I_{ct}/I_{cc})/K_{ZE} + I_{tc}/I_{tt})/(2\tau_m)$. *I*_{xx} denotes the peak integrals from the 2D NOESY spectra with the first subscript indicating the *F*₁ frequency (either *cis* or *trans*) and the second the *F*₂ frequency. At each temperature the NOESY mixing times *τ*_m were chosen such that *I*_{ct} ≪ *I*_{cc} and *I*_{tc} ≪ *I*_{tt}. Activation enthalpy and entropy for the *cis*→*trans* and *trans*→*cis* isomerization were obtained from Eyring plots according to $\ln(k/T) = (-\Delta H^0/R)(1/T) + \Delta S^0/R + \ln(k_B/h)$.

Conformational analysis: The pucker of the proline ring was identified in analogy to the work by Gerig and McLeod^[7] by the distinct pattern of the ¹H–¹H and ¹H–¹⁹F coupling constants observed in 1D-¹H and 1D-¹⁹F NMR spectra; for example, the γ-*exo*-pucker results in large and similar coupling constants *J*(H_α,H_{β1}) and *J*(H_α,H_{β2}), whereas for the *endo*-pucker one of the coupling constants is large and the other is small. Similarly, also other couplings show characteristic patterns for the *endo*- and *exo*-pucker, respectively.

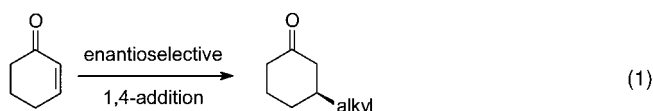
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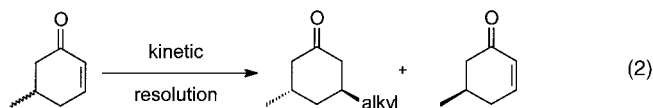
Highly Enantioselective Copper–Phosphoramidite Catalyzed Kinetic Resolution of Chiral 2-Cyclohexenones**

Robert Naasz, Leggy A. Arnold, Adriaan J. Minnaard, and Ben L. Feringa*

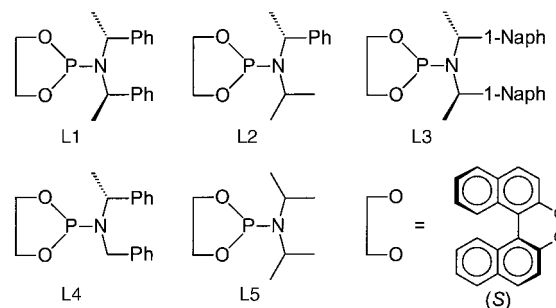
Chiral 2-cyclohexenones are attractive building blocks for the synthesis of a variety of natural products. A limited number of naturally occurring optically active cyclohexenones such as pulegone, piperitone, and carvone are cheap, readily available, and widely used for this purpose.^[1] The development of routes to other optically active 2-cyclohexenones includes the preparation of nonnatural cyclohexenones from naturally occurring ones; for example, 4-methyl- and 5-methylcyclohexenone can be derived from pulegone and carvone.^[2] Recently the groups of Corey and Sato introduced elegant methods for the synthesis of enantiomerically pure 2-cyclohexenones which can easily be converted into a variety of other chiral 2-cyclohexenones.^[3] Although both methods are widely applicable they consist of multistep syntheses to obtain the desired 2-cyclohexenone synthons. On the other hand a variety of racemic 2-cyclohexenones is readily accessible. This encouraged us to develop a general method towards optically active 2-cyclohexenones by kinetic resolution of racemic 2-cyclohexenones based on the copper–phosphoramidite catalyzed 1,4-addition to enones [Eq. (1)].^[4]



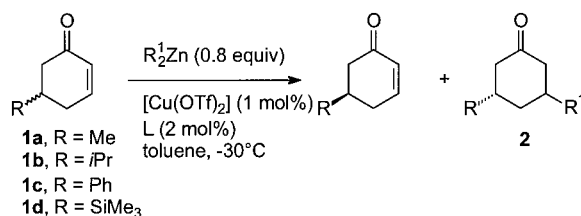
It was anticipated that the high enantioselectivity obtained with these catalysts in the 1,4-addition of diethylzinc to 2-cyclohexenone (>98% *ee*, [Eq. (1)]),^[4] combined with the high *trans*-diastereoselectivity generally found in the addition of organometallic reagents to, for example, 5-alkyl-substituted 2-cyclohexenones,^[5] should provide high selectivity in the kinetic resolution of such compounds [Eq. (2)].^[6, 7]



To check the viability of this new approach we tested the ligands L1–L5 in the kinetic resolution of racemic 5-substituted 2-cyclohexenones **1a–d** under the conditions typical



for the asymmetric 1,4-addition as shown in Scheme 1. By using [Cu(OTf)₂] (1 mol %), (*S,R,R*)-L1 (2 mol %), and Et₂Zn (0.8 equiv) in toluene at –40 °C for the resolution of (±)-5-methyl-2-cyclohexenone (**1a**) on a 1 mmol scale, an *ee* of 88%



was reached at 48% conversion indicating a selectivity (*s*) of 120 (Table 1, entry 1).^[8–10] Accordingly after 20 min 53% conversion had taken place and unreacted **1a** with 99% *ee* was found. This high selectivity makes the resolution synthetically applicable.^[11] Based on the expected *trans*-diastereoselectivity and the fact that the 1,4-addition of Et₂Zn to 2-cyclohexenone in the presence of L1 produces (*S*)-3-ethylcyclohexanone we predicted the unreacted enantiomer to be (*R*)-**1a** which turned out to be correct.^[4d, 5, 12]

A good correlation was observed between the results with the ligands L1–L5 in the 1,4-addition of diethylzinc to 2-cyclohexenone and the results in the kinetic resolution (Table 1, entries 1–9). The most successful ligands in the 1,4-addition, namely (*S,R,R*)-L1, (*S,R*)- and (*S,S*)-L2 (Table 1, entries 3 and 4), and (*S,R,R*)-L3 (Table 1, entry 5), also give the highest selectivity in the kinetic resolution of **1a**.^[4b] Noteworthy is the fact that (*S,R,R*)-L1 gives a much faster reaction at –40 °C than all other ligands at –30 °C, reaching 48% conversion after only 15 min.^[13] This finding and the high selectivity obtained with (*S,R,R*)-L1 make it the obvious ligand of choice in these kinetic resolution experiments. The high activity of this catalyst also makes resolutions on a larger scale with lower catalyst loading possible. To demonstrate this a resolution experiment was performed on **1a** (11.0 g, 100 mmol) with [Cu(OTf)₂] (18.1 mg, 0.05 mol %), (*S,R,R*)-L1 (54 mg, 0.10 mol %), and 0.55 equivalents of Et₂Zn. Aqueous work up followed by column chromatography

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

Table 1. Kinetic resolution of 5-substituted 2-cyclohexenones **1a–d** according to Scheme 1.

Entry	Ligand	Enone	R ¹	t [min]	Conv. [%] ^[a]	ee [%] ^[a]	s	Conf. ^[b]
1 ^[c]	(<i>S,R,R</i>)-L1	1a	Et	15	48	88	120	<i>R</i>
		20			53	99		
2	(<i>S,S,S</i>)-L1	1a	Et	15	42	62	24	<i>R</i>
3	(<i>S,R</i>)-L2	1a	Et	90	49	86	50	<i>R</i>
4	(<i>S,S</i>)-L2	1a	Et	45	51	90	42	<i>R</i>
5	(<i>S,R,R</i>)-L3	1a	Et	45	46	76	40	<i>R</i>
6	(<i>S,S,S</i>)-L3	1a	Et	90	19	12	3	<i>R</i>
7	(<i>S,R</i>)-L4	1a	Et	45	55	84	14	<i>R</i>
8	(<i>S,S</i>)-L4	1a	Et	60	62	75	6	<i>R</i>
9	(<i>S</i>)-L5	1a	Et	90	27	22	5	<i>R</i>
10	(<i>S,R,R</i>)-L1	1b	Et	10	54	96	39	–
11	(<i>S,R,R</i>)-L1	1c	Et	–	55	89 ^[d]	19	<i>R</i>
12	(<i>S,R,R</i>)-L1	1d	Et	5	56	86	14	–
13	(<i>S,R,R</i>)-L1	1a	<i>i</i> Pr	60	55	84	14	<i>R</i>
14 ^[e]	(<i>S,R,R</i>)-L1	1a	<i>n</i> Bu	15	49	93	> 200	<i>R</i>
		30			54	> 99		
15 ^[e]	(<i>S,R,R</i>)-L1	1b	<i>n</i> Bu	60	50	93	94	–
		90			53	99		
16 ^[e]	(<i>S,R,R</i>)-L1	1d	<i>n</i> Bu	15	44	78	> 200	–
		45			52	> 99		
17 ^[e]	(<i>S,R,R</i>)-L1	1a	Me	20	50	93	94	<i>R</i>
18 ^[e]	(<i>S,R,R</i>)-L1	1b	Me	25	48	85	66	<i>R</i>
19 ^[e]	(<i>S,R,R</i>)-L1	1d	Me	15	50	90	58	–

[a] Both conversion and *ee* determined by chiral GC in the presence of *n*-dodecane or *n*-hexadecane as internal standard (see Supporting Information). [b] Configuration of the unconverted enone. [c] Reaction run at –40 °C. [d] *ee* determined by chiral HPLC (see Supporting Information). [e] Reaction run at –35 °C.

yielded (*R*)-**1a** (3.6 g; 33 %) with an *ee* > 99%.^[14] ¹³C NMR analysis of the isolated product **2** (R = Me, R¹ = Et) showed the presence of >95 % of the *trans* diastereomer.^[15]

Because the relatively small methyl group in **1a** already gives rise to high selectivity we expected that other 5-substituted substrates would also give selectivities high enough to be synthetically useful.^[16] To our surprise a more bulky isopropyl group (**1b**) led to a slight decrease in the selectivity (*s* = 39; Table 1, entry 10), and substrate **1c** containing a phenyl group at the 5-position also gave a lower selectivity (*s* = 19; Table 1, entry 11) than **1a**. Resolution of the synthetically important 5-trimethylsilyl-2-cyclohexenone (**1d**) was also successful, providing 86 % *ee* at 56 % conversion (*s* = 14, Table 1, entry 12).^[3a, 16b, 17]

We next turned our attention to the influence of the dialkylzinc reagent on the enantioselectivity in the kinetic resolution. We reasoned that using the more bulky *i*Pr₂Zn reagent in the resolution of **1a** would lead to an even higher selectivity for the *trans* product than Et₂Zn, and consequently would give a higher *s* value. Surprisingly the opposite was observed and the selectivity decreased drastically to *s* = 14 (Table 1, compare entries 1 and 13). On the other hand the use of *n*Bu₂Zn led to a significant increase in selectivity to *s* > 200, showing that an *ee* of 99 % is reached at 51 % conversion (Table 1, entry 14). The results for the kinetic resolution of **1a** with different zinc reagents are graphically summarized in Figure 1.

To our delight the selectivity was higher with *n*Bu₂Zn than with Et₂Zn (Table 1, entries 15 and 16) for both substrates **1b** and **1d**. In particular a remarkable increase in selectivity from *s* = 14 with Et₂Zn to *s* > 200 with *n*Bu₂Zn was observed for

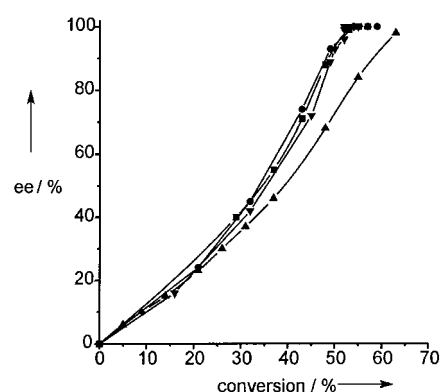


Figure 1. Plot of *ee* [%] against conversion [%] for the kinetic resolution of **1a** with (*S,R,R*)-L1, [Cu(OTf)₂] and Et₂Zn (■), *i*Pr₂Zn (△), *n*Bu₂Zn (●), and Me₂Zn (▼) (entries 1, 13, 14, and 17 in Table 1).

synthon **1d**. The use of Me₂Zn also gave excellent selectivities in the resolution of **1a**, **1b**, and **1d** (Table 1, entries 17–19). In a number of enzymatic kinetic resolutions a fast and stereo-selective reaction of one enantiomer of the racemic substrate takes place, while the other is not converted even after prolonged reaction.^[18] We approach this near perfect situation in the kinetic resolution of **1a** as the reaction virtually ceases at 50 % conversion (Figure 2) in the presence of one equivalent of Me₂Zn, which makes it easy to stop the reaction at the optimal conversion and *ee*.^[19]

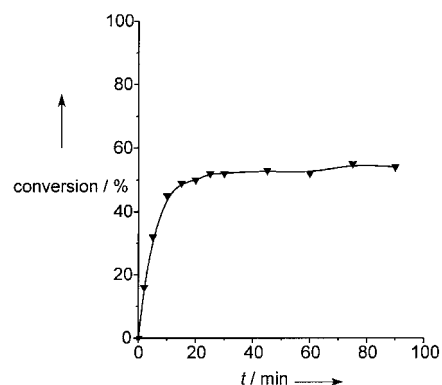
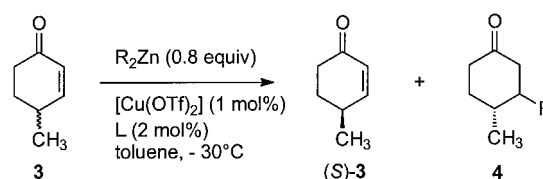


Figure 2. Plot of conversion [%] against time *t* for the kinetic resolution of **1a** with (*S,R,R*)-L1, [Cu(OTf)₂], and Me₂Zn (entry 17 in Table 1).

The results of the kinetic resolution of racemic 4-methyl-2-cyclohexenone (**3**) (Scheme 2) are summarized in Table 2.^[8, 20] The selectivity was lower than that observed for most of the 5-substituted 2-cyclohexenones as could be expected from the lower *trans* selectivity in the 1,4-addition to 4-substituted 2-cyclohexenones.^[15] Again (*S,R,R*)-L1 was the most successful ligand with *s* = 16 but in this case the peculiar observation was made that (*S,S,S*)-L1 performed nearly as well (*s* = 13),



Scheme 2. Kinetic resolution of racemic 4-methyl-2-cyclohexenone (**3**).

Table 2. Kinetic resolution of **3** according to Scheme 2.

Entry	Ligand	R	t [min]	Conv. [%] ^[a]	ee [%] ^[a]	s
1 ^[b]	(S,R,R)-L1	Et	15	48	71	16
2	(S,S,S)-L1	Et	60	55	83	13
3	(S,R,R) + (S,S,S)-L1 (1:1)	Et	30	52	78	17
4	(S,R)-L2	Et	105	57	81	10
5	(S,S)-L2	Et	75	56	85	13
6	(S,R,R)-L4	Et	105	54	83	15
7	(S,R,R)-L4	Et	120	19	10	3
8 ^[c]	(S,R,R)-L1	Me	75	58	82	10
9 ^[c]	(S,R,R)-L1	nBu	25	45	70	27

[a] Both conversion and ee determined by chiral GC in the presence of *n*-dodecane as internal standard (see Supporting Information). [b] Reaction performed at -40°C . [c] Reaction performed at -35°C .

whereas the resolution with a 1:1 mixture of the two diastereomers of L1 gave a selectivity of 17 (Table 2, entries 1–3). The use of Me_2Zn instead of Et_2Zn led to a slight decrease in selectivity, whereas again the use of $n\text{Bu}_2\text{Zn}$ led to an increase in selectivity to $s = 27$ (Table 2, entries 8 and 9).

The high selectivities (s up to and above 200) obtained with the [(S,R,R)-L1-Cu(OTf)₂] complex in the catalytic kinetic resolution of **1a–d** and **3** make this an excellent method for obtaining these valuable building blocks with an $ee > 99\%$. Furthermore the high selectivity and high activity of this catalyst enabled us to successfully perform a resolution of **1a** on a multigram scale.

Experimental Section

Resolution of racemic **1a** on 100 mmol scale: In flame-dried glassware under an argon atmosphere [Cu(OTf)₂] (18 mg, 0.05 mmol) and (S,R,R)-L1 (54 mg, 0.10 mmol) were dissolved in dry toluene (100 mL). After stirring at room temperature for 1 h the colorless solution was cooled to -30°C and racemic **1a** (11.0 g, 100 mmol) and *n*-dodecane (4.0 mL) were added. After the mixture had been stirred for 10 min, Et_2Zn (50 mL of 1.1 M solution in toluene, 55 mmol) was added dropwise by syringe over 5 min. A sample (0.1 mL) was taken after reaction overnight and analyzed by chiral GC (see Supporting Information) showing **1a** with 93% ee at 51% conversion. Extra Et_2Zn (3.6 mL, 1.1 M solution in toluene) was added and after 3 h another sample was taken. GC analysis showed $>99\%$ ee and 55% conversion. The reaction mixture was quenched with 1 M HCl aq (150 mL), and the aqueous layer was extracted with Et_2O ($3 \times 100\text{ mL}$), and the combined organic layers were washed with brine and dried over Na_2SO_4 . Filtration and evaporation of the solvents yielded a mixture of **1a**, addition product, and *n*-dodecane which were separated by column chromatography (SiO_2 , hexanes/diethyl ether 4:1) to give (R)-(-)-**1a** (3.6 g, 33 mmol, 33%). $[\alpha]_D^{20} = -87.3^{\circ}$ ($c = 0.81$, CHCl_3).^[3b] ^1H NMR (200 MHz, CDCl_3): $\delta = 1.06$ (d, $J = 6.1\text{ Hz}$, 3H), 1.9–2.5 (m, 5H), 6.0 (m, 1H), 6.9 (m, 1H); ^{13}C NMR (300 MHz, CDCl_3): $\delta = 21.06$ (q), 30.20 (d), 33.87 (t), 46.12 (t), 129.44 (d), 149.80 (d), 199.93 (s). GC analysis (Chiraldex G-TA) showed an $ee > 99\%$ (no (S)-**1a** was detected).

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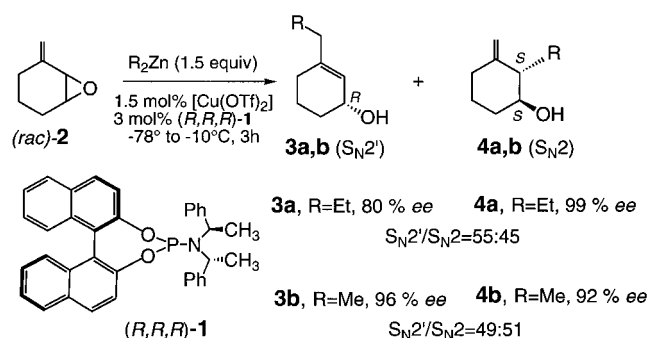
Highly Enantioselective Regiodivergent and Catalytic Parallel Kinetic Resolution**

Fabio Bertozzi, Paolo Crotti, Franco Macchia, Mauro Pineschi,* and Ben L. Feringa*

The development of new methodologies for the preparation of chiral compounds of high optical purity by means of asymmetric catalysis is presently an area of great importance in organic chemistry. Kinetic resolution of a racemic mixture with a chiral reagent is a well-documented strategy in which a maximum of only one half of the racemic starting material is converted into non-racemic products.^[1] Parallel kinetic resolution (PKR) is an interesting strategy recently introduced, in which both enantiomers of a racemate can be converted into useful products.^[2] This conceptual variation often requires the use of two different stoichiometric chiral reagents in parallel.^[3] Parallel reactions under non-stoichiometric conditions have previously been described in the asymmetric Bayer–Villiger oxidation of racemic ketones, by means of enzymatic methods^[4] or chiral catalysts,^[5] and in the intramolecular cyclopropanation of racemic allylic diazoacetates catalyzed by chiral rhodium complexes.^[6] The latter is the only example of a PKR reaction involving the formation of a C–C bond. In this special case, there are distinct reactivities for both enantiomers: one enantiomer gave intramolecular cyclopropanation, whereas the other enantiomer was transformed by means of a hydride abstraction/elimination into achiral compounds.

Herein we report the first highly stereocontrolled transformation of a racemic mixture by an organometallic reagent and a chiral catalyst to give separable regioisomeric products.

Recently, we described a new catalytic kinetic resolution of racemic vinyloxiranes with dialkylzinc reagents (0.50 equiv) by using copper complexes of non-racemic phosphoramidite as chiral catalysts.^[7a] When racemic vinyl epoxide **2** was treated with excess Et_2Zn (1.5 equiv) in the presence of the catalyst prepared in situ from $[\text{Cu}(\text{OTf})_2]$ (1.5 mol %) (Tf = triflate = OSO_2CF_3) and (*R,R,R*)-**1** (3 mol %), complete conversion of **2** took place in 3 h to give, after usual work-up and chromatographic purification (see Experimental Section), the corresponding $\text{S}_{\text{N}}2'$ -addition product (*R*)-**3a** (46 % yield, 80 % *ee*; Scheme 1) together with the regioisomeric alcohol



Scheme 1. Enantioselective and regiodivergent addition of R_2Zn to racemic **2** catalyzed by $[\text{Cu}(\text{OTf})_2]/(\text{R},\text{R},\text{R})$ -**1**.

(1*S*,2*S*)-**4a** (37 % yield) having a surprising 99 % *ee*! The progress of the reaction in terms of the the conversion and enantioselectivities (Figure 1a and 1b, respectively) was therefore closely monitored.^[8] The peculiarity of this reaction stems from the fact that regioisomeric products were derived from opposite enantiomers of **2** in two clearly distinct phases: The first one was very fast, proceeding with $\text{S}_{\text{N}}2'$ -regioselectivity to yield (*R*)-**3a** (15 min at -78°C), whereas the second slower one which provided (1*S*,2*S*)-**4a** (-10°C and 3 h to go to completion) exhibited a complementary $\text{S}_{\text{N}}2$ regioselectivity. In fact, after 15 min at -78°C , the remaining vinyloxirane (1*S*,2*R*)-**2** (62 % conversion) was enantiomerically pure, ($>98\%$ *ee*)^[9] and it reacted with nearly complete regioselectivity, and with complete *anti* stereoselectivity, at the 2-position. The catalyzed addition of Me_2Zn followed an even more pronounced regiodivergent behavior, affording, after complete conversion of **2**, (*R*)-**3b** (49 % GC yield, 96 % *ee*) and (1*S*,2*S*)-**4b** (51 % GC yield, 92 % *ee*) (Scheme 1).

The complementary enantiomer-dependent regioselectivity was also demonstrated by a reaction carried out with the racemic catalyst (*R,R,R*)(*S,S,S*)-**1**. In this case, the conjugate-addition product **3** was obtained with almost complete regioselectivity ($\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2 = 98:2$), clearly indicating that chiral recognition leads to enantio- and regiodivergent reactivity when the reaction is performed with the chiral catalyst.

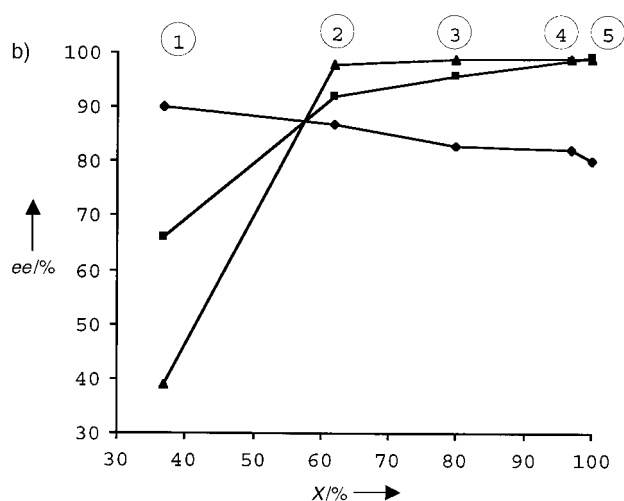
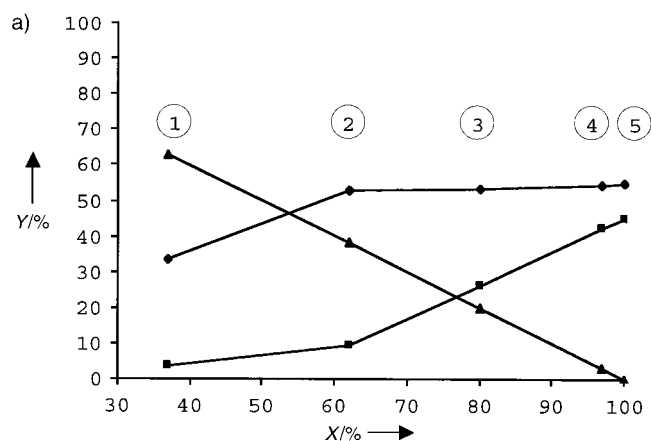
The mechanism for the copper-catalyzed organometallic addition reactions has been discussed in a number of reports.^[10] Probably the initially formed π complex **2A**^{[11][12]} undergoes an oxidative addition resulting in the formation of

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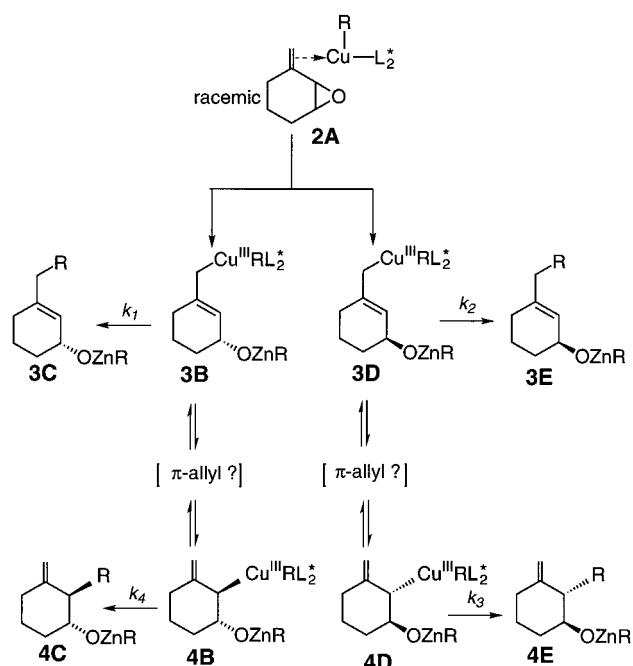
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	1	2	3	4	5
<i>t</i> [min]	3	15	120	150	180
<i>T</i> [°C]	-78	-78	-55	-35	-10

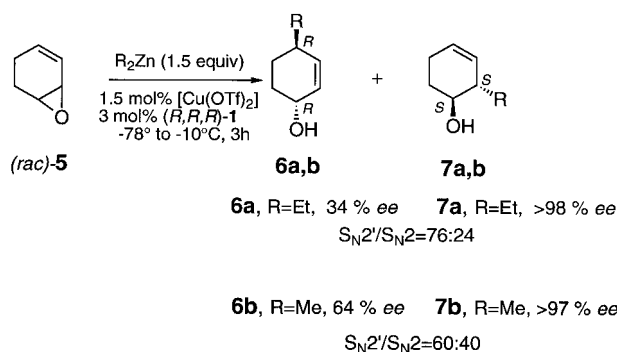
Figure 1. GC yield *Y* [%] (a) and enantiomeric excesses [%] (b) of compounds **2** (▲), **3a** (◆), **4a** (■) present in the reaction mixture at different conversions *X* of **2**. Values determined by GC using a β -cyclodextrin column (see Supporting Information).

(σ -allyl)copper(III) species **3B** and **3D** (Scheme 2). It is proposed that the regioselectivity of the reaction depends on the relative rates of reductive elimination from diastereoisomeric complexes **3B** and **3D**, and isomerization to (σ -allyl)copper(III) complexes **4B** and **4D**, respectively, (through a π -allyl complex or a 1,3-sigmatropic rearrangement) with subsequent reductive elimination.^[13] The fast reductive elimination (k_1) of **3B** without concomitant isomerization could account for the nearly complete conversion of (1*R*,2*S*)-**2** into S_N2' -adduct **3C**. Probably, the slower corresponding reductive elimination (k_2) from **3D** allows an isomerization to the regioisomeric complex **4D** which undergoes a faster (k_3) reductive elimination to afford a large amount of S_N2 -adduct **4E** with a high *ee*. Evidently, the acceleration of the C–C bond formation by the chiral ligand is unequal for complexes **3B,D** and **4B,D**, thus affording the observed stereo- and regioselectivity.^[14]



Scheme 2. Postulated mechanism of the regiodivergent PKR.

The efficient catalytic conversion of a racemic compound to two different and separable chiral products of high isomeric purity has been accomplished also by the use of a vinyloxirane having a blocked *s-cis* conformation such as 1,3-cyclohexadiene monoepoxide **5** (Scheme 3). The addition of Me_2Zn



Scheme 3. Enantioselective and regiodivergent addition of R_2Zn to racemic **5** catalyzed by $[\text{Cu}(\text{OTf})_2]/(R,R,R)\text{-1}$.

(1.5 equiv) to ($\pm$)-**5** catalyzed by $[\text{Cu}(\text{OTf})_2]/(R,R,R)\text{-1}$ afforded a 60:40 mixture of (+)-(1*R*,4*R*)-**6b** (S_N2' -adduct, 64 % *ee*) and (1*S*,2*S*)-**7b** (S_N2 -adduct, >97 % *ee*).^[15] The catalyzed addition of Et_2Zn (1.5 equiv) to the same racemate afforded a 76:24 mixture of regioisomer (+)-(1*R*,4*R*)-**6a** (34 % *ee*) and (+)-(1*S*,2*S*)-**7a** (>98 % *ee*). Evidently with this substrate, while keeping the corresponding $k_1 \gg k_4$ for one enantiomer of the substrate, the rates of reductive elimination versus isomerization for the other one (k_2 vs. k_3 of Scheme 2) are not very different, thus allowing the formation of regioisomeric S_N2 adducts **7a, b** with very high *ee*, together with large amounts of S_N2' substitution products **6a, b** with a reduced enantioselectivity.

The mechanism of this reaction and the exact nature of the copper species involved in this highly efficient catalytic process still need to be established. Nevertheless, this unprecedented regiodivergent catalytic parallel kinetic resolution with an organometallic reagent supports the notion that the oxidative addition might be a very fast process and reductive elimination is instead a regio- and stereodetermining step.

Experimental Section

General procedure: A solution of $[\text{Cu}(\text{OTf})_2]$ (10.83 mg, 0.030 mmol) and **1** (32.3 mg, 0.06 mmol) in anhydrous toluene (4.0 mL) was stirred at room temperature for 40 min. The colorless solution was cooled to -78°C , and subsequently solutions of racemic vinyl epoxide (2.0 mmol) in toluene (1.0 mL) and R_2Zn (3.0 mmol) in toluene were added. The resulting light yellow solution was quenched with saturated aqueous NH_4Cl (5.0 mL) once the reaction reached completion (GC analysis). Extraction with Et_2O and evaporation of the dried (MgSO_4) organic phase gave the crude product, which was subjected to flash chromatography (see Supporting Information). Enantioselectivities were determined by chiral GC (CP-cyclodextrin- β -column).

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From Oligomers to Conducting Polymers of the Metal–Dinitrogen Functionality**

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This report opens, in the use of dinitrogen, a completely new avenue, which is derived neither from any of the bioinspired processes^[1] nor from the objectives pursued so far in the metal-assisted dinitrogen chemistry.^[2, 3]

Although $\text{:N}\equiv\text{N:}$ and $[\text{:C}\equiv\text{C:}]^{2-}$, the deprotonated form of acetylene, are isoelectronic, this similarity has not helped in establishing a practical parallelism between the two species, namely in the triple bond cleavage^[2b–i] or in their use in material science. In the latter context, the polymeric forms of acetylene, such as polyacetylene and related cumulenes, have a relevant importance.^[4, 5] This report deals with the oligomerization of the metalla–dinitrogen functionality and with a perspective to polymerize this moiety. This entry into material science using dinitrogen opens a new avenue in this domain. We report herein how we were able to achieve the unprecedented oligomerization of the metalla–dinitrogen functionality and thereby anticipating and planning the formation of the corresponding polymers.

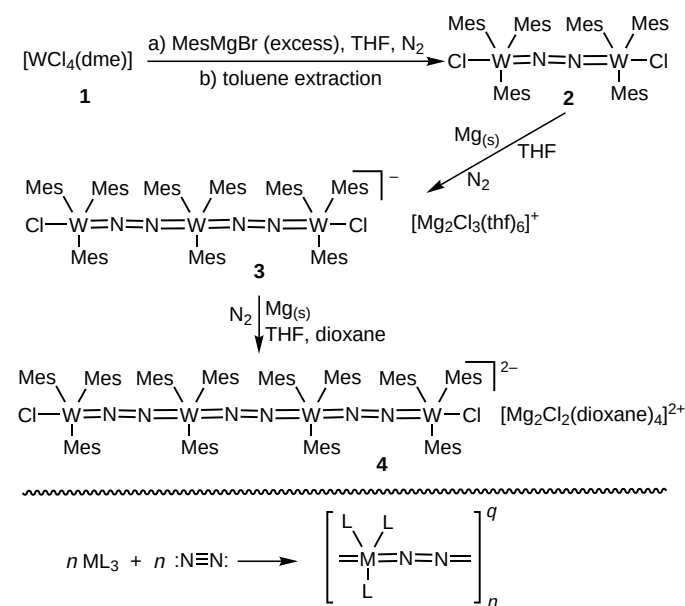
The alkylation of $[\text{WCl}_4(\text{dme})]$ (DME = dimethoxyethane) using MesMgBr ($\text{Mes} = 2,4,6\text{-(CH}_3)_3\text{C}_6\text{H}_2$) under a nitrogen atmosphere occurs with a fast absorption of dinitrogen

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leading to the intermediate formation of a red solid, which was then extracted with toluene, thus producing **2** as a diamagnetic, green crystalline material (Scheme 1). Complex



Scheme 1. Preparation of compounds **2–4**.

2 was fully characterized both in solution and in the solid state (W–N 1.846(8), N–N 1.180(16) Å; W–N–N = 180.0°). Complex **2** undergoes a stepwise reduction under N₂ atmosphere leading to **3**^[6] and then to **4** (Scheme 1), as controlled by the W/Mg stoichiometric ratio. The occurrence of the reaction can be followed by the expected absorption of N₂ and a change in the color of the solution from green (**2**) to red (**3**) and then to violet (**4**). Both **3** and **4** are diamagnetic, so that the conversion of a dinuclear → trinuclear → tetranuclear dinitrogen compound can be followed by ¹H NMR. The most relevant structural parameters of **3** are represented by the bond length sequence W–N 1.787(7), N–N 1.272(10), N–W 1.881(7), W–N 1.861(7), N–N 1.273(11), and N–W 1.801(7) Å, while those of **4** are in the caption of Figure 1.^[7] Although there are significant differences in the W–N and N–N bond distances for **2**, **3**, and **4** depending on the oligomerization degree, these structural parameters are in reasonable agreement with the proposed cumulene structure.^[2f–i, 8, 9] The tungsten–dinitrogen oligomers can be seen as chains with two perpendicular π-systems made of alternating metal and two nitrogen atoms and carrying two electrons for each nitrogen atom and the d electrons of tungsten. Each one of these systems therefore resembles the π-system of an organic polyene, with as many carbon atoms as the total number of tungsten and nitrogen atoms in the considered oligomer. The calculations performed on the dinuclear, trinuclear, and tetranuclear

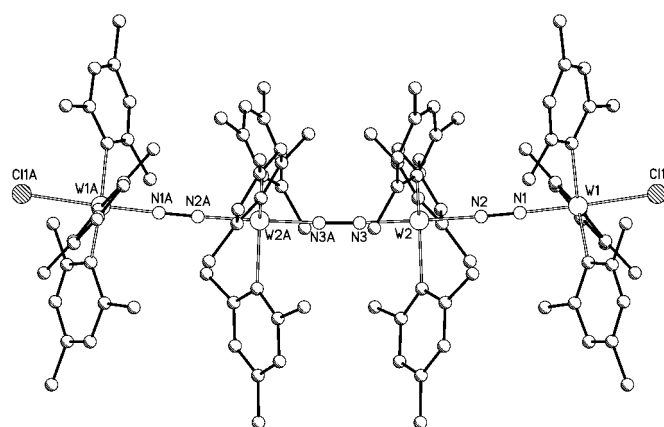


Figure 1. Ball-and-stick diagram for the anion in complex **4**. Selected bond lengths [Å] and angles [°]: W1–Cl1 2.494(2), W1–N1 1.825(8), W1–C_{av} 2.145(10), N1–N2 1.212(12), W2–N2 1.931(7), W2–N3 1.855(8), W2–C_{av} 2.166(9), N3–N3A 1.264(15); Cl1–W1–N1 177.9(2), W1–N1–N2 178.8(7), N1–N2–W2 177.9(7), N2–W2–N3 178.8(3), W2–N3–N3A 177.4(4). The notation A indicates the symmetry transformation $-x+1, y, -z+\frac{1}{2}$.

species show a stable singlet state with a large HOMO–LUMO gap.

The sequence displayed in Scheme 1 anticipates the existence and the electronic structure of hypothetical metalladinitrogen polymers, for which a strong theoretical support is presented here. We have used the extended-Hückel method in the tight-binding scheme^[10] to study the electronic structure of the $[-(\text{H})_3\text{W–N}_2-]_n^q$ hypothetical polymers, **5**, with different electron counts obtained by varying the charge of the $[(\text{H})_3\text{W}]$ metal fragment.^[11] In particular, we considered d², d³, or d⁴ metal configurations corresponding to $[-(\text{H})_3\text{W–N}_2-]_n^{q+}$, $[-(\text{H})_3\text{W–N}_2-]_n^q$, and $[-(\text{H})_3\text{W–N}_2-]_n^{q-}$ polymers. The energy levels for the planar WL₃ fragment show the usual pattern expected for a D_{3h} symmetry. At the lowest energies, there is an e set, of predominantly metal d_{xy} and d_{yz} character, a slightly higher a₁(d_{z²}), and then a second e set of predominantly metal d_{x²–y²} and d_{xz} character, much higher in energy. The band structure of the considered polymer is shown in Figure 2a, where only the highest occupied and lowest unoccupied crystal orbitals are reported and the Fermi level is referred to a d² configuration. The projection of the d metal and carbon p_x and p_y orbitals (the z-axis is assumed to be parallel to the axis of the polymers) of the density of states (DOS) for **5**, Figures 2b and 2c, clarify the nature of these bands. The main feature of the band structure is the presence

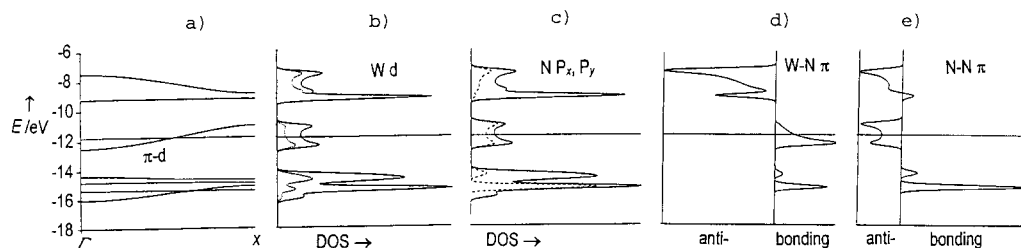


Figure 2. a) Band structures of the $[-(\text{H})_3\text{W–N}_2-]_n^q$ polymer. b, c) Density of states (solid lines) with the projection of the b) metal d orbitals and c) N p_x and p_y orbitals (dashed lines). d, e) Crystal-orbital overlap population (COOP) curves for d) N–N and e) W–N π-bonding. The horizontal lines indicate the Fermi energy for the $[-(\text{H})_3\text{W–N}_2-]_n^{q+}$ polymer with d² metal configuration.

of an occupied, high lying, dispersed band arising from the interaction of the e (d_{xz} , d_{yz}) set and the π^* orbitals of the dinitrogen unit (hereafter called π -d band) with W–N bonding and N–N antibonding character, as shown by the crystal-orbital overlap population (COOP) curves, Figures 2d and 2e. The next lowest occupied crystal orbitals have a high contribution from the occupied σ - and π -orbitals of the N_2 moiety, while the lowest unoccupied crystal orbital is a flat band of essentially metal e (d_{xy} , $d_{x^2-y^2}$) character (see Figure 2b).

For a $[-(H)_3W-N_2-]_n^{n+}$ polymer, with a formal d^2 configuration of the tungsten centers, the π -d band is half filled, so that this species is predicted to show a partial cumulene structure as well as conducting properties. However, for this simple linear system, we expect a pairing Peierls distortion, which would open a band gap at the Fermi level and lead to an alternate $[-W\equiv N-N\equiv W-N\equiv N-]_n^{n+}$ character superimposed on the cumulene structure.

The π -d band is completely filled in the $[-(H)_3W-N_2-]_n^{n-}$ polymer as the tungsten has a d^4 configuration. In such a case, a stable nonconducting species with a cumulene structure is expected to exist. However, this highly anionic species may easily undergo a partial oxidation leading to a conducting doped polymer.

For the neutral $[-(H)_3W-N_2-]_n$ polymer, with a formal tungsten d^3 configuration, the π -d band is three-quarters filled and only a tetrameric distortion is expected to open a band gap at the Fermi level. Since the driving force for the distortion drops off with the size of the distorted unit cell,^[12] a lower tendency to Peierls distortion is expected, so that this polymer could show conducting properties.

Our preliminary results anticipate the real possibility of making polymers with relevant physical properties out of dinitrogen.

Experimental Section

2: A THF solution (170 mL) of MesMgBr (188.7 mmol) was added dropwise under N_2 to a suspension of $[WCl_4(dme)]$ (19.6 g, 47.0 mmol) in THF (150 mL) cooled to $-10^\circ C$. The suspension was stirred and left overnight to warm slowly to room temperature. The resulting red solid (19.0 g) was suspended in toluene and refluxed for 2 h. The final brown-green solution was filtered while hot. The resulting solution was left overnight at room temperature and a crystalline, brown-green solid formed (9.30 g, 29%). ^1H NMR (200 MHz, $[D_6]benzene$, $25^\circ C$, TMS): δ = 6.76 (s, 6H; CH), 6.60 (s, 6H; CH), 2.64 (s, 18H; CH_3), 2.29 (s, 18H; CH_3), 1.98 (s, 18H; CH_3); UV/Vis (toluene): λ_{max} (ϵ) = 320 nm ($18715 M^{-1} cm^{-1}$); elemental analysis for $2 \cdot C_7H_8$ [%]: calcd $C_{61}H_{74}Cl_2N_2W_2$ (1273.8): C 57.52, H 5.85, N 2.20; found: C 57.50, H 5.96, N 1.67.

The X-ray analysis was performed on green crystals of **4**. A brown THF suspension (400 mL) of $2 \cdot C_7H_8$ (6.40 g, 5.02 mmol) was treated with activated Mg metal (0.174 g, 7.15 mmol). The suspension, stirred overnight under N_2 at room temperature, gave a red solution, which turned deep-violet. The addition of dioxane (50 mL) caused the partial precipitation of $MgCl_2$. The suspension was then filtered. The resulting violet solution was evaporated to dryness and the solid collected with n -hexane (100 mL) (4.74 g, 70%). ^1H NMR (400 MHz, $[D_6]benzene$, $25^\circ C$, TMS): δ = 6.82 (s, 6H; CH), 6.66 (s, 6H; CH), 6.52 (s, 12H; CH), 2.60 (s, 18H; CH_3), 2.31 (s, 18H; CH_3), 2.24 (s, 18H; CH_3), 2.11 (s, 36H; CH_3), 1.91 (s, 18H; CH_3); UV/Vis (toluene): λ_{max} (ϵ) = 558 nm ($46736 M^{-1} cm^{-1}$); elemental analysis for $4 \cdot MgCl_2$ [%]: calcd $C_{124}H_{164}Cl_6Mg_3N_6O_8W_4$ (2887.6): C 51.57, H 5.72, N 2.91; found C 51.60, H 5.77, N 2.86.

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Hydrogen Bond in Molecules with Large-Amplitude Motions: A Rotational Study of Trimethylene Sulfide...HCl**

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In four-membered ring compounds, the various intramolecular forces determine both the conformation and the dynamics of the large-amplitude ring-puckering motions.^[1] The conformation is described by the potential function for the out-of-plane vibration (ring puckering) and depends on the balance between two large opposing forces. The first of these is the classical ring strain, which tends to make the molecule planar. The second is the torsional force associated with adjacent CH₂ groups, which tends to pucker the ring. If the ring strain dominates, the potential function contains a single minimum at the planar conformation, while if the torsional force is predominant, the potential function has a double minimum with a barrier at the planar conformation.

The trimethylene sulfide (thietane) ring undergoes a large-amplitude ring-puckering motion. The associated potential function has a double minimum with a barrier to the planar conformation of 274(2) cm⁻¹ [2, 3] (Figure 1 a). Tunneling motion through this barrier interconverts the isoenergetic,

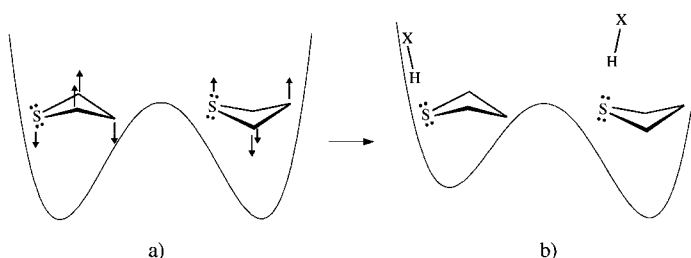


Figure 1. Ring-puckering potential functions for a) trimethylene sulfide and b) the trimethylene sulfide...HCl complex. The potential function of the complex is speculative.

puckered trimethylene sulfide (TMS) conformers and makes equivalent the nonbonding electron pairs at the sulfur atom, which can act as proton acceptors. When complexed with a hydrogen halide HX (X = F, Cl) in the gas phase, a question arises: Is the ring puckering such a prominent large-amplitude motion in TMS that it prevails also in its hydrogen-bonded complexes? If the double minimum is retained after complex-

ation, the interaction of HX with the lone pairs at S would result exceptionally in two different axial and equatorial complexes, since the two nonbonding electron pairs were not equivalent. These conformations would have different energies and could be observed as structurally different species in an asymmetric double-minimum potential function (Figure 1 b).

In order to clarify this situation, we have undertaken a study of the complex formed between TMS and HCl. The experimental study has been carried out in the collisionless environment of a supersonic jet, where the complexes are easily formed and can be characterized by Fourier-transform microwave spectroscopy. The high sensitivity of this technique makes it possible to isolate and observe the axial and equatorial conformers which could be formed in the supersonic expansion.

Initial predictions of the rotational spectrum for both axial and equatorial conformers were obtained considering a C_s symmetry with the HCl molecule^[4] located in the symmetry plane of TMS^[5] at bond angles and distances taken from the related complex tetrahydrothiophene...HCl.^[6] From this model, the two conformers of TMS...HCl were predicted to be nearly prolate asymmetric tops with their dipole moments oriented along the *a* and *b* principal inertial axes. A planar conformation of TMS giving rise to only one conformer for the complex was also considered. Using mixtures with argon as carrier gas, several groups of lines were detected and identified as corresponding to ^aR branch transitions of the axial conformer. No sign of the equatorial conformer was observed employing argon as carrier gas. When TMS and HCl were diluted in helium, less intense new bands appeared along with those attributed to the axial form in the regions previously scanned and they were readily assigned to the equatorial conformer. The assignment of both conformers was completed with the measurement of *b* type transitions. The spectra of several isotopic species were also detected and assigned for both forms.

Recently, axial and equatorial hydrogen bond complexes have been also reported for tetrahydropyran...HCl,^[7] thiane...HCl,^[8] and tetrahydropyran...HF.^[9] In these cases, the existence of two nonequivalent pairs of lone electrons at the oxygen or sulfur atoms is a consequence of the structure of the acceptor molecule itself. In the present case, the equivalence of the nonbonding pairs at sulfur is broken by effect of complexation. The observation of the axial and equatorial conformers in the TMS...HCl complex constitutes the first experimental evidence of the implication of a large-amplitude motion in the conformational behaviour of a complex.

All observed rotational transitions showed a quadrupole hyperfine structure due to the presence of a chlorine nucleus. The frequencies (available as Supporting Information) were fitted^[10] to a Hamiltonian including the semirigid-rotor terms of the Watson Hamiltonian in the A reduction and the I' representation^[11] and the quadrupole coupling terms.^[12] The associated observable parameters are the rotational (*A*, *B*, *C*) and centrifugal distortion constants (*Δ_J*, *Δ_{JK}*, *Δ_K*, *δ_J*, *δ_K*), and the elements of the quadrupole coupling tensor (*χ_{ij}*; *i*, *j* = *a*, *b*, *c*), respectively. The spectroscopic constants obtained from this analysis are listed in Tables 1 and 2.

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

Table 1. Spectroscopic constants for axial TMS...HCl.

	C ₃ H ₆ ³² S...H ³⁵ Cl	C ₃ H ₆ ³² S...H ³⁷ Cl	C ₃ H ₆ ³² S...D ³⁵ Cl	C ₃ H ₆ ³⁴ S...H ³⁵ Cl	α - ¹³ C ¹² C ₂ H ₆ ³² S...H ³⁵ Cl	β - ¹³ C ¹² C ₂ H ₆ ³² S...H ³⁵ Cl
<i>A</i> [MHz]	4457.5910(27) ^[a]	4457.0074(41)	4446.6646(19)	4377.42(17)	4402.44(27)	4384.08(24)
<i>B</i> [MHz]	1437.25677(62)	1392.8089(11)	1431.2428(11)	1429.95245(39)	1424.91556(66)	1431.48978(80)
<i>C</i> [MHz]	1341.24209(61)	1302.4054(11)	1335.0355(10)	1327.52957(42)	1334.64141(68)	1329.49502(82)
Δ_J [kHz]	1.7653(32)	1.6762(43)	1.7429(47)	1.6975(88)	1.756(14)	1.757(18)
Δ_{JK} [kHz]	15.491(19)	14.770(39)	15.279(35)	[15.491] ^[b]	[15.491]	[15.491]
Δ_K [kHz]	−14.34(47)	−13.25(69)	[−14.34]	[−14.34]	[−14.34]	[−14.34]
δ_J [kHz]	0.1570(28)	0.1439(42)	0.1543(40)	[0.1570]	[0.1570]	[0.1570]
δ_K [kHz]	−4.87(22)	−4.85(42)	−4.81(48)	[−4.87]	[−4.87]	[−4.87]
χ_{aa} [MHz]	−35.8240(79)	−28.3140(72)	−36.560(11)	−36.347(43)	−35.682(88)	−35.41(10)
$(\chi_{bb} - \chi_{cc})$ [MHz]	−16.376(12)	−12.831(14)	−16.701(14)	−15.826(67)	−16.44(19)	−16.89(20)
$ \chi_{ab} $ [MHz]	32.05(46)	25.21(63)	32.78(52)	[32.05]	[32.05]	[32.05]
<i>N</i> ^[c]	145	111	111	39	23	19
<i>J</i> _{max}	8	7	7	6	5	5
σ ^[d] [kHz]	1.8	1.6	2.5	1.3	2.3	1.8
<i>P</i> _c ^[e] [u Å ²]	44.10160(70)	44.10173(88)	44.10377(80)	44.0919(28)	45.4027(42)	44.0958(39)

[a] Standard error in parentheses in units of the last digit. [b] Parameters in square brackets were fixed to the C₃H₆³²S...H³⁵Cl value. [c] Number of fitted quadrupole components. [d] Root mean square deviation of the fit. [e] $P_c = (I_a + I_b - I_c)/2 = \sum_i m_i r_i^2$. Conversion factor: 505 379.1 MHz u Å².

Table 2. Spectroscopic constants for equatorial TMS...HCl.

	C ₃ H ₆ ³² S...H ³⁵ Cl	C ₃ H ₆ ³² S...H ³⁷ Cl	C ₃ H ₆ ³² S...D ³⁵ Cl	C ₃ H ₆ ³⁴ S...H ³⁵ Cl
<i>A</i> [MHz]	4753.9408(19) ^[a]	4750.7390(30)	4738.3168(19)	4661.36(25)
<i>B</i> [MHz]	1354.88137(77)	1313.6645(18)	1349.71417(99)	1349.95623(42)
<i>C</i> [MHz]	1289.97569(73)	1252.3321(18)	1284.15074(97)	1278.57039(42)
Δ_J [kHz]	1.9645(29)	1.8595(42)	1.9447(30)	1.8908(72)
Δ_{JK} [kHz]	−0.524(25)	−0.526(39)	−0.753(32)	[−0.524]
Δ_K [kHz]	13.14(32)	[13.14] ^[b]	[13.14]	[13.14]
δ_J [kHz]	0.2228(22)	0.2043(27)	0.2250(29)	[0.2228]
δ_K [kHz]	2.04(33)	2.42(84)	2.17(46)	[2.04]
χ_{aa} [MHz]	−30.131(10)	−23.932(12)	−30.757(15)	−30.614(46)
$(\chi_{bb} - \chi_{cc})$ [MHz]	−22.700(12)	−17.710(18)	−23.156(18)	−22.27(14)
$ \chi_{ab} $ [MHz]	35.844(35)	28.19(17)	36.584(50)	[35.844]
<i>N</i> ^[c]	148	113	113	35
<i>J</i> _{max}	9	7	7	6
σ ^[d] [kHz]	1.6	1.8	1.9	2.3
<i>P</i> _c ^[e] [u Å ²]	43.76972(76)	43.7690(11)	43.77044(83)	43.7585(35)

[a]–[e] See footnotes to Table 1.

The first necessary step in the structural analysis is the experimental confirmation of the previously assumed C_s symmetry for the conformers. The near invariance of the planar moments *P*_c (see Tables 1 and 2) for the isotopic substitution of nuclei in the symmetry plane and the fact that these values are nearly equal to *P*_b of free TMS (*P*_b = 43.98299(16) u Å², calculated from data given in ref. [3]) are conclusive pieces of evidence that both conformers have C_s symmetry. The structures of both conformers given in Table 3 were determined from fits to the corresponding sets of rotational constants given in Tables 1 and 2. The angle α_{az} (Figure 2), which defines the position of the H atom of the HCl subunit, has been obtained from the values of the elements of the quadrupole coupling tensor.^[6, 13] For the equatorial conformer, the parameters of the TMS ring were held fixed to those obtained for the axial conformer. It can be noted that the ring-puckering angle of TMS in the complex ($\gamma = 24(2)^\circ$) is close to that of free TMS ($\gamma = 28^\circ$).^[2]

Several aspects on the axial and equatorial structures can be discussed. The hydrogen bond parameters *r*(S...H) and φ are practically identical for both conformers. If we consider the

Table 3. Structural parameters concerning the hydrogen bond.^[a]

	axial	equatorial
<i>r</i> (S–C _α) [Å]	1.82(2) ^[b]	[1.82] ^[c]
<i>r</i> (C _α –C _β) [Å]	1.56(3)	[1.56]
<i>r</i> (C _α –C _γ) [Å]	2.287(5)	[2.287]
γ [°]	24(2)	[24]
<i>r</i> (S...Cl) [Å]	3.539(8)	3.50(3)
ϕ [°]	87.0(7)	84.5(15)
∠CSC [°]	77.7(11)	–
<i>r</i> (S...H) [Å]	2.28(2)	2.26(6)
φ [°]	92.1(10)	91.1(17)
θ [°]	14.1(8)	18.4(5)

[a] See Figure 2 for symbol definitions. [b] Standard error in parentheses in units of the last digit. [c] Parameters in square brackets were kept fixed in the fit.

HCl molecule as a probe for the direction of the nonbonding electron pairs, these results strongly suggest that these lone pairs are located symmetrically with respect to the CSC plane of TMS at angles of about 90°. This can be rationalized considering the HOMO–LUMO model, which interprets the

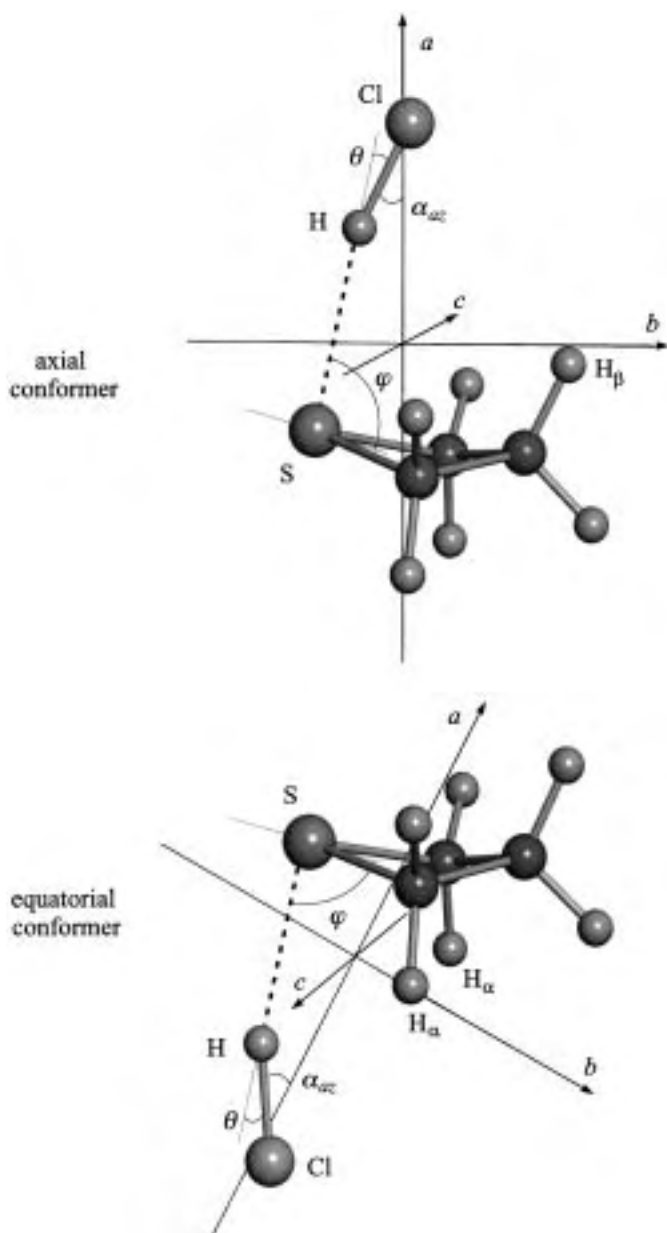


Figure 2. Structures of axial and equatorial conformers of TMS...HCl.

new bond as an interaction between the σ^* LUMO orbital of HCl and the n_π HOMO orbital of TMS, orthogonal to the S-C bonds. These results can also be understood in terms of the valence shell electron-pair repulsion (VSEPR) model,^[14] from which an angle between the lone electron pairs larger than tetrahedral would be expected.

Another structural aspect to discuss is the remarkable deviation from the collinear arrangement of the S...H-Cl atoms shown by both conformers, reflected in the value of θ (see Figure 2). These deviations can be attributed to the existence of secondary hydrogen bonds between the chlorine atom and the nearest H atoms of the methylene groups.^[6, 8, 13] The calculated distances $r(\text{Cl}\cdots\text{H}_\beta) = 3.20$ and $r(\text{Cl}\cdots\text{H}_\alpha) = 3.26$ Å for the axial and the equatorial conformers, respectively, lie in the range reported for related complexes.^[6, 8, 13, 15]

An interesting fact is the relaxation from the equatorial to the axial conformer observed in the supersonic expansion.

When argon is used as carrier gas, the intensity ratio of about 2.5:1 between axial and equatorial conformers observed with helium does not prevail and only the axial form is detected. This proves conclusively that this form is the most stable one. It is commonly accepted that a heavy inert gas produces a relaxation from the high-energy conformer to the most stable one when the interconversion barrier between them is lower than a certain value (about 400 cm^{-1}).^[16] In our case, the interconversion between axial and equatorial conformers can only take place through the paths sketched in Figure 3. The

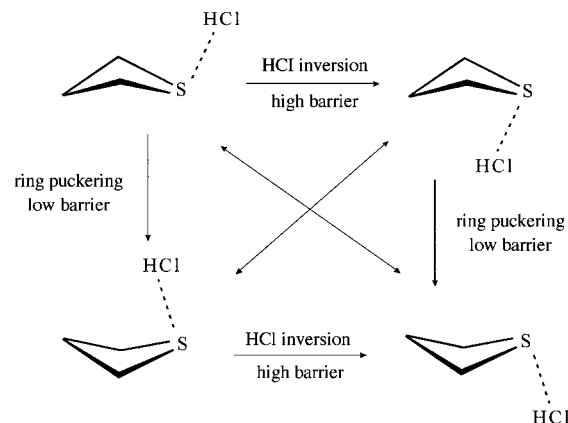


Figure 3. Possible interconversion paths between the axial and equatorial conformers of TMS...HCl.

HCl inversion motion can be excluded, since the angle between the lone pairs (ca. 180°) implies a high barrier to interconversion as in the thiane...HCl complex,^[8] for which relaxation has not been observed. Consequently, the interconversion should occur via ring puckering, so the ring inversion barrier remains at a low value in the complex. Thus, we can conclude that the large-amplitude ring-puckering motion is not substantially altered by hydrogen bond formation.

We believe that these experimental results constitute a keystone for future studies on the implication of large-amplitude motions in hydrogen bonding. We are carrying out further investigations in order to shed more light on this problem.

Experimental Section

The rotational spectra of the axial and equatorial conformers of TMS...HCl, generated in a supersonic jet, have been observed by Fourier-transform microwave spectroscopy (frequency range 5–18.5 GHz).^[17] The complexes were formed by expanding gas mixtures of TMS (ca. 1%, Aldrich) and HCl (ca. 4%, Aldrich) or DCl (ca. 4%, Euriso-top) in either Ar or He (1–2 bar) through a pulsed nozzle into a vacuum chamber. Molecular pulses of 0.3–0.35 ms were macroscopically polarized by microwave pulses of about 0.2 μs within the Fabry–Pérot cavity. The rotational spectra were obtained as the Fourier transformation of the relaxation signal in the time domain.

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Revolutionizing Resin Handling for Combinatorial Synthesis

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The last decade has seen rapid growth both in combinatorial methodology and technology development.^[1] Traditionally, resin beads have been handled as a free-flowing material, which although relatively simple for the synthesis of single compounds, does complicate the handling issues for large numbers of single compounds in multiple parallel synthesis. The major advances in this area; tea-bags,^[2] crowns,^[3] and Irori Kans^[4] methodology permit the production and handling of discrete packets of resin materials for multiple parallel synthesis, although even here the filling, sealing, labeling of

the units and the recovery of tagging devices complicates handling and have cost implications. More recent innovations include the monolithic polymer discs of Sherrington et al.,^[5] which were then used by a number of other workers.^[6]

We now report a fundamentally new approach to resin handling. The method is applicable to various resin types (polystyrene (PS), polystyrene–polyethyleneglycol graft polymer (PS-PEG)), either pre- or postloaded with virtually any linker or linker-scaffold combinations. The method is applicable to all routinely used resin bead sizes and substitutions. The approach can be used to generate individual resin-based supports in virtually any shape or form desired, and makes resin much more convenient to handle, yet maintains the original chemical properties of the resin.

The basis of this new method is resin sintering within an inert polymer matrix.^[7] This was achieved by blending appropriate proportions, in this case 1:1, of ultra-high molecular weight polyethylene and the synthesis resin, to a homogeneous mix. This was then loaded into polytetrafluoroethylene (PTFE)-lined moulds and passed through a sintering oven under a nitrogen atmosphere. The temperature of the mixture was gradually increased as it passed through the oven, just to the point where the polyolefin matrix began to soften (determined experimentally). The moulds were then gradually cooled and the formed plugs ejected from the mould. The plugs were made in a cylindrical form, as this shape fitted nicely into the wells of a 96-well plate. This shape also combines ease of preparation of the mould with the physical strength of the plug. Plugs could however be made in a variety of different shapes or sizes, with an upper limit determined by the necessity for reasonably low-temperature gradients between the inside and outside of the plug during the sintering process. Various structural features such as handles, holes, or struts can be in-built for improving the ease of handling or increasing the strength of the shape by changing the mould. The cylindrical plugs made were 9 mm long, 7.5 mm diameter and had a mass of (170 ± 6) mg resulting in a very defined loading per plug. A typical plug contained 50% synthesis resin, which approximates to 85 mg of Merrifield resin (initially 0.96 mmol g^{-1}) thereby giving an initial loading of $81.6 \mu\text{mol}$ per plug. The plugs are porous, with solvent able to freely access through the pores of the matrix of the plug and into the synthesis resin held therein. This was demonstrated by soaking a plug in a solution of bromophenol blue in dichloromethane and then slicing the plug to ascertain the loading of the dye. Within one minute the dye had entered the polyethylene (PE) plug although presumably it would take longer to reach all the reactive sites. The plugs produced are solid devices in which the beads are intact and are physically attached to the polyethylene filler by a small amount of polymer flow onto the beads (Figure 1). Clearly, a proportion of resin bead is physically prevented from reacting freely, but this is small and only on the surface and thus insignificant. These plugs in effect function as minireactors.

A feature of these devices is the relative freedom from the well-known swelling properties of all manner of gel based resins. We attribute this to the void volume within the plug, and the flexibility of the internal structure allowing an

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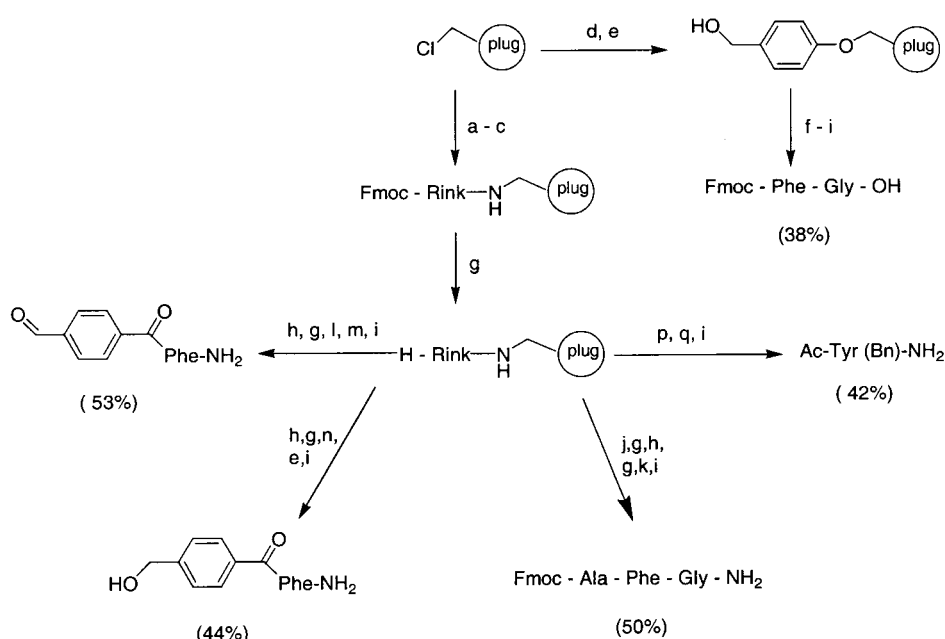
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Figure 1. a) Cross-section of resin plug (100 $\times$ magnification). b) Single bead within the matrix of resin plug (270 $\times$ magnification). c) Illustration of dimensions of resin plug (9 mm long, 7.5 mm diameter).

element of “breathing” which accommodates within the device framework any swelling that occurs. There was only an approximately 20% increase in the volume of a plug when swollen in DMF. The structural integrity of the new support was checked in a wide range of organic solvents normally used in solid-phase organic synthesis (SPOS), both at room temperature and with heating. They were stable in all solvents with the exception of hot toluene (which is known to soften polyethylene) and maintained both their original shape and size. The plugs were also treated for two hours at room temperature with a variety of acids (trifluoroacetic acid (TFA), 2 M HCl) and bases (piperidine, triethylamine, 2 M NaOH) and were perfectly stable. The plugs were robust towards magnetic stirring, mechanical shaking, centrifugation, and the application of a vacuum. Washing the plugs to release a dye, did require a slightly longer time than loose resin (1.5 times), although like Irori Kans the process was accelerated by the application of a vacuum. Mechanical losses from the surface were negligible and only noticeable at the first swelling/reaction of the plugs. The resin plugs were found to require longer reaction times than loose resin (double the time). They also took longer to wash than loose resin.

Applications: Initially, resin plugs were prepared with Merrifield Resin and were converted into the aminomethylated form by using potassium phthalimide followed by hydrazine to give a measured loading^[8] of 56 μmol per plug. The plugs were then loaded with the Fmoc-Rink-amide linker^[9] and a number of standard chemistries/cleavages (Scheme 1) performed on this new material in parallel with identical chemistry carried out on loose resin. These initial chemistries included: oxidation, reduction, Mitsunobu's, and



Scheme 1. Chemistries done on resin plugs (figures shown represent yields of isolated products). a) Potassium phthalimide (5 equiv), DMF, 120 °C, 16 h; b) H_2NNH_2 (10 equiv), EtOH, reflux, 5 h; c) Fmoc-Rink-OH (1.5 equiv), DIC (1.5 equiv), HOBT (1.5 equiv), CH_2Cl_2 , 24 h; d) 4-hydroxybenzaldehyde (10 equiv), K_2CO_3 (10 equiv), MeCN, reflux, 48 h; e) NaBH_3CN , MeOH, 6 h; f) Fmoc-Gly-OH (5 equiv), DIC (5 equiv), DMAP (0.2 equiv); g) 20% piperidine/DMF, 20 min; h) Fmoc-Phe-OH (5 equiv), DIC (5 equiv), HOBT (5 equiv); i) 95% TFA; j) Fmoc-Gly-OH (5 equiv), DIC (5 equiv), HOBT (5 equiv); k) Fmoc-Ala-OH (5 equiv), DIC (5 equiv), HOBT (5 equiv); l) 4-hydroxymethylbenzoic acid (5 equiv), DIC (5 equiv), HOBT (5 equiv); m) $\text{PySO}_3/\text{DMSO}$ (10 equiv), Et_3N (10 equiv); n) 4-formylbenzoic acid (5 equiv), DIC (5 equiv), HOBT (5 equiv), 16 h; p) Ac-Tyr-OH (5 equiv), DIC (5 equiv), HOBT (5 equiv), 6 h; q) PhCH_2OH (10 equiv), PPh_3 (5 equiv), DEAD (5 equiv), THF, 2 h. DIC = diisopropylcarbodiimide, HOBT = 1-hydroxy-1H-benzotriazole, Py = Pyridine, TFA = trifluoroacetic acid, DEAD = diethylazodicarboxylate, Bn = benzyl.

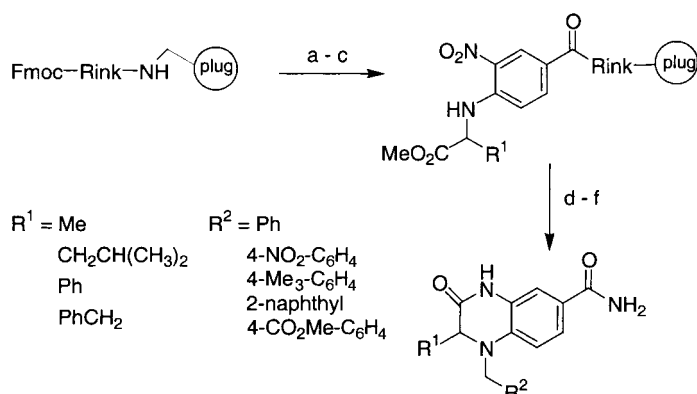
peptide synthesis. The results of these chemistries were very similar to those obtained on loose resin carried out in parallel. The resin plugs were also derivatized with a Wang linker and used to synthesize a dipeptide in the standard manner (Scheme 1).

To test the general applicability of the method, nine different resin types were sintered and a number of different chemistries carried out on the plugs and compared with identical loose resin. The results are summarized in Table 1. In all cases, the results were virtually identical, and considering our limited experience of handling the plugs at this stage, very encouraging.

Synthesis of three small libraries: A number of small libraries was then prepared on the resin plugs. Initially a small library of biaryl derivatives was constructed (Scheme 2).

average purity of 90–95 % (HPLC) was observed for the sulfonamides, amides, and ureas, falling to 80–90 % for the tertiary amines. The weight recovery per plug for each purified compound was good and ranged between 5–12 mg. Based on the starting plug loading, the overall yields of cleaved purified materials were 36–86 %.

A third small library of 3,4-disubstituted 7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-ones was prepared on the resin plugs. The synthesis (Scheme 4) was adapted from the literature.^[11] A representative compound (Table 3, entry 9) was isolated with an overall yield of 40 % (literature, 48 %). The average crude product purity by HPLC was 52 %.



Scheme 4. Library of 3,4-disubstituted 7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-ones. a) 20 % piperidine/DMF, 20 min; b) (4-F,3-NO₂)PhCOCl (5 equiv), DIPEA (5 equiv); c) H₂NCH(R¹)CO₂Me (10 equiv), DIPEA (10 equiv), DMF, 3 days; d) SnCl₂·H₂O (20 equiv), DMF, 3 days; e) R²CH₂Br (25 equiv), K₂CO₃ (25 equiv), (CH₃)₂CO, reflux, 48 h; f) 95 % TFA.

Table 3. Library of 3,4-disubstituted 7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-ones.

Entry	R ¹	R ²	HPLC purity [%]
1	Me	Ph	69
2	Me	4-Me-C ₆ H ₄	43
3	Me	2-naphthyl	39
4	CH ₂ CH(CH ₃) ₂	Ph	42
5	CH ₂ CH(CH ₃) ₂	2-naphthyl	52
6	CH ₂ CH(CH ₃) ₂	4-CO ₂ Me-C ₆ H ₄	59
7	Ph	Ph	44
8	Ph	4-Me-C ₆ H ₄	75
9	CH ₂ Ph	4-Me-C ₆ H ₄	40
10	CH ₂ Ph	2-naphthyl	57

In summary, we have developed a new method of resin handling. Considering the huge effort in the area of solid-phase synthesis and solution chemistry using resin scavengers/reagents, the approach of resin sintering offers a cheap and readily available method of preparing discrete, easy to handle, encoded materials for multiple parallel synthesis, defined mix and split synthesis and scavenging/immobilized reagents, in whatever formats are deemed appropriate, and with any resin desired. We are currently investigating the use of resin plugs in further reactions and their use as scavengers, supported reagents and catalysts and will communicate our results in due course.

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Adsorption-Mediated Electrochemical Sensing of Halides**

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Measurements of halide concentrations are crucial in many clinical and environmental analyses and in many areas of industrial chemistry.^[1] Ion-selective electrodes (ISEs) have been increasingly used for monitoring the concentrations of many ions such as halides.^[2, 3] These electrodes incorporate a solid membrane that allows the selective diffusion of one ion to its surface to produce an electrochemical potential that is proportional to the concentration of the ion in solution.

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Commercial halide-ISEs often exhibit an interference by ions such as CN^- , S^{2-} , SCN^- , and other halides, and show a selectivity for the target ion that is far from specific. Despite efforts to optimize the properties of these electrodes, ISEs continue to face two principal limitations,^[2, 3] namely 1) erroneous signals from ions that either compete with the target ion in the detection process or that form a precipitate on the membrane surface and block access to the electrode by the ion of interest, and 2) a modest level of sensitivity that requires concentrations of 0.5 to 10 μM for detection. The use of luminescent dyes and a combination of absorption and fluorescence measurements has been recently reported as an alternative method for monitoring chloride concentrations;^[4] however, such approaches are sensitive to changes in pH and are susceptible to photobleaching.

Herein we report that underpotentially deposited (upd) Ag adlayers on Au surfaces can provide a means to measure Cl^- , Br^- , and I^- concentrations in a manner that offers several advantages over present electrochemical methods of detection. These Ag adlayers are easily prepared by an electroplating process^[5] and provide the ability by a single electrode to identify each of these halides and to quantify their concentrations in aqueous solutions. These electrodes show a higher sensitivity for measuring halide concentrations than provided by most conventional detection systems.

The basis for halide detection is an effected electrochemical change to the Ag upd layer on Au(111) by halide adsorption.^[6, 7] Figure 1 schematically illustrates various stages during the adsorption process for chloride ions onto a Ag upd adlayer on Au(111) and its effected electrochemical changes to the modified electrode. Herein we focus on the detection of chloride for simplicity; however, related results were obtained from experiments performed by using bromide and iodide. In

this process, the chloride ions adsorb spontaneously onto the Au/Ag(upd) electrode surface, and cause replacement of the native Ag stripping peak at 535 mV versus Ag^+/Ag^0 by a stripping peak at 615 mV that can be assigned to the formation of Au/Ag(upd)-Cl. Notably, the adsorption of chloride onto the Ag adlayer shifts the stripping potential for the affected Ag adatoms by about 80 mV. The adsorption of the halide onto the Au(111)/Ag(upd) electrode surface produces temporal variations in the relative integrated charge densities for the peaks at 535 and 615 mV that correlate with the amount of adsorbed chloride, and their ratio can be related to the concentration of chloride in the test solution (see below).

Figure 2 shows kinetic data for the conversion of a fresh Au(111)/Ag(upd) sample to Au(111)/Ag(upd)-Cl for various

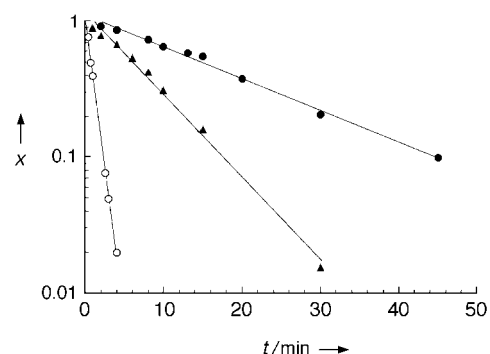


Figure 2. Kinetic data for the conversion of the native Ag upd layer to its halide-derivatized state for various contact times with 0.5 ($\bullet$), 1.0 ($\blacktriangle$), and 10 ($\circ$) μM KCl(aq) test solutions. The three data sets exhibit a first-order decay in the fractional intensity of the unconverted Ag(upd)/Au(111) signal (x), and the rates of conversion across these data sets vary linearly with their halide concentration.

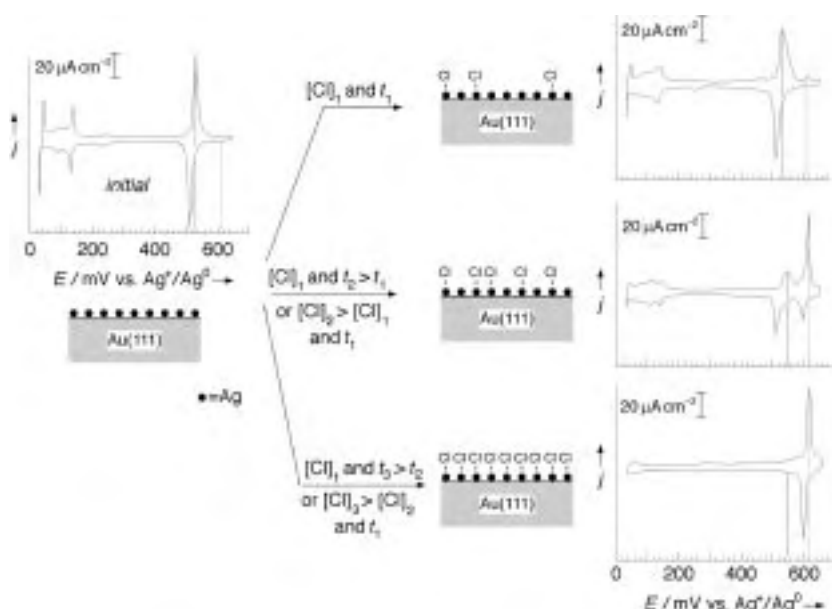


Figure 1. Schematic illustration of various stages during the adsorption of chloride onto a Ag upd layer on Au(111) and its effected electrochemical changes as monitored by cyclic voltammetry in 0.6 mM $\text{Ag}_2\text{SO}_4/0.5\text{ M H}_2\text{SO}_4(\text{aq})$. The stripping peak at 535 mV (initial Ag upd system, solid line) is stochastically replaced by a peak at 615 mV versus Ag^+/Ag^0 as a result of chloride adsorption (dashed line). $[\text{Cl}]_1 - [\text{Cl}]_3$ are different times of exposure of the electrode.

contact times with 0.5, 1.0, and 10 μM KCl(aq) solutions. A first-order process fits the data well, and the rate constants determined from the slopes of these fits scaled linearly with the halide concentration. These data provide the basis for quantifying Cl^- concentrations in an aqueous solution through Equation (1), where I

$$\ln \left(\frac{I_{\text{Au/Ag(upd)}}}{I_{\text{Au/Ag(upd)}} + I_{\text{Au/Ag(upd)-halide}}} \right) = -k_{\text{halide}} C_{\text{halide}} t \quad (1)$$

is the integrated intensity of a stripping peak, k_{halide} is a rate constant for halide adsorption, C_{halide} is the solution halide concentration, and t is the time the Au(111)/Ag(upd) electrode is exposed to the halide solution. Using Equation (1), we were able to determine the chloride concentrations across a variety of test solutions. For more concentrated solutions (such as a commercial sample of concentrated nitric acid with ca. 5 ppm of Cl^-), a 1000 $\times$ dilution with water was required for analysis using a contact time of 1 min. In contrast, to measure the chloride content in a sample of deionized water (18.2 M Ω), a contact time of 1 h was required to

produce a 20% conversion to the chloride-related stripping peak, corresponding to a measured chloride concentration of about 80 nM. By these methods, we were able to demonstrate the ability of the Ag upd adlayer to measure trace amounts of chloride (including those in the ppt range) across a variety of conditions. In addition, the method was suitable for detecting such low concentrations of Cl^- in solutions that also contained 0.5 M of NO_3^- , SO_4^{2-} , or PO_4^{3-} ions, and in those at acidic pH.

We also examined the effect of Br^- and I^- adsorption on the electrochemical stripping behavior of Au/Ag(upd) electrodes. Figure 3 contains cyclic voltammograms (CVs) for fully

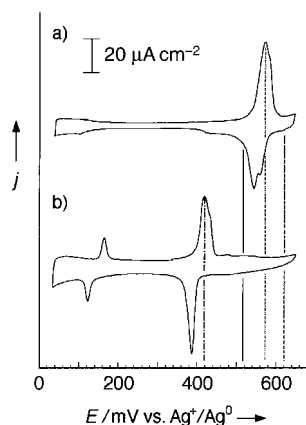


Figure 3. Cyclic voltammograms for the upd and stripping of Ag adlayers on Au(111) electrodes that were pretreated with a) Br^- and b) I^- . The adsorption of these halides each produces different changes to the cyclic voltammogram. The adsorption of Br^- onto the Ag adatoms increased the Ag upd stripping potential to 575 mV versus Ag^+/Ag^0 (dotted line), while the adsorption of I^- decreased the Ag upd stripping potential to ~ 415 mV (dotted-dashed line). The additional lines at 535 and 615 mV indicate the Ag upd stripping potentials for native (solid line) and Cl^- -covered Ag adatoms (dashed line), respectively.

converted Au/Ag(upd)-Br and Au/Ag(upd)-I electrodes showing that the adsorption of these halides each produced distinct features in the CV that replaced the original deposition and stripping peaks of the native Ag upd adlayer. Specifically, the adsorption of Br^- onto the Ag adatoms increased the Ag upd stripping potential by about 40 mV to 575 mV versus Ag^+/Ag^0 , while the adsorption of I^- decreased this potential by about 120 mV to ~ 415 mV. These differences in potential across Cl^- , Br^- , and I^- provide a direct means for identifying each of these solution-phase halides. Further, the adsorption kinetics for Br^- and I^- onto the Au/Ag(upd) surface showed a similar first-order behavior as for Cl^- adsorption (Figure 2),^[8] and the amounts of adsorbed Br^- and I^- could be measured by simple integration of the stripping peaks for the native and reacted Ag adatoms and related to solution concentrations through use of Equation (1).

The detection limit by the Au/Ag(upd) electrodes for chloride (and for bromide and iodide) is determined by the contact time between the electrode and the test solution. From a practical standpoint, a conversion of 2–3% of the Ag atoms on the Au electrode to Au/Ag(upd)-Cl (that is, ca. 50 pmoles of adsorbed Cl^- per cm^2) is necessary to produce a clearly distinguishable electrochemical signal for

the Au/Ag(upd)-Cl peak that is needed for determining the chloride solution concentration [Eq. (1)]. Longer contact times increased the measured surface concentrations of adsorbed chloride on the electrode (as evidenced by an increase in the signal at 615 mV) effecting a decrease in the detection limit for the halide. For example, contact times of 1 and 10 min provided detection limits for Cl^- of 500 and 50 nM, respectively,^[9] where the trade-off between contact time and concentration was inversely related as expected for a first-order reaction process. Detection limits for Br^- and I^- under these conditions were similarly in the submicromolar regime.

A notable feature of this strategy using the Au(111)/Ag(upd) surface for quantifying halide concentrations is its ability to produce distinguishable signals for Cl^- , Br^- , and I^- that provide their identification.^[10] We note that a current challenge for this method (as it is for many other strategies) is that the presence of other halides, when present at a similar or higher concentration as the halide of interest, complicates measurements of concentration by the electrode. For example, Figure 4 shows a CV for a Au/Ag(upd) sample after contact for 1 min with a solution containing 2.5 μM KCl and

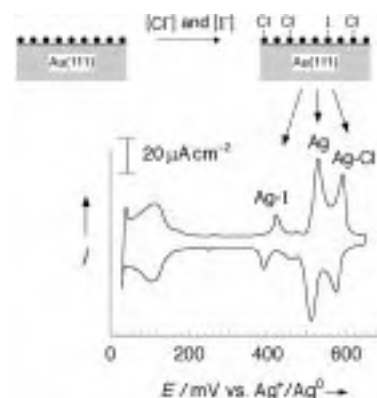


Figure 4. Cyclic voltammogram for a Au/Ag(upd) sample in 0.6 mM $\text{Ag}_2\text{SO}_4/0.5$ M $\text{H}_2\text{SO}_4(\text{aq})$ after contact with a solution containing 2.5 μM KCl/2.5 μM KI(aq) for 1 min. The CV exhibits three distinct stripping peaks for the Ag upd layer that identify the presence of Cl^- and I^- in the test solution. The temporal variations in these three stripping peaks are likely to provide an ability by these Au/Ag(upd) electrodes to detect and measure the concentrations of multiple halides.

2.5 μM KI. The CV exhibits three distinct stripping peaks for the Ag upd layer at about 415, 535, and 615 mV versus Ag^+/Ag^0 , that can be readily assigned to Au/Ag(upd)-I, Au/Ag(upd), and Au/Ag(upd)-Cl, respectively. The electrode clearly provides information that the solution contains both Cl^- and I^- ,^[11] but the presence of both species complicates their measurement by a simple analysis. For example, the concentration of both chloride and iodide in solution was equal; however, the intensity of the peak for Ag-Cl was significantly greater than that for Ag-I. The difference between the halide concentrations on the electrode surface and in solution results from a difference in their affinities for the electrode surface and a competition for adsorption sites by the two ions. A description of these processes is likely to result from an examination of the kinetic and thermodynamic factors underlying the adsorption processes for these halides,

and we are presently conducting such studies. With this information, we expect that the present strategy using Au/Ag(upd) electrodes for halide detection will provide the notable abilities to measure the concentrations of multiple halides simultaneously and to provide specific signals for confirming their identification.

Experimental Section

Materials: Au (99.99%) shot and Cr-coated tungsten filaments were obtained from Americana Precious Metals (East Rutherford, NJ) and R. D. Mathis (Long, Beach, CA), respectively. Sulfuric acid (double distilled, 98%) and silver sulfate ($c(\text{Cl}^-) \leq 0.02\%$) were obtained from Aldrich and used as received. KCl, KBr, and KI were obtained from Mallinckrodt and used as received. Au(111) samples were prepared by sequential evaporation of Cr (2–3 nm) and Au (150 nm) onto glass slides and a post-evaporation annealing in a hydrogen flame.^[12]

Electrochemical measurements: Cyclic voltammetry was conducted with a computer-controlled PAR Model 263A potentiostat. A solution of 0.6 mM Ag_2SO_4 and 0.1M H_2SO_4 in deionized water (Millipore, 18.2 M Ω) was used to deposit the Ag upd adlayer on gold. Modified electrodes were prepared by cycling once in this solution and being removed at a 300 mV versus Ag^+/Ag^0 under potentiostatic control.^[13] The Au(111)/Ag(upd) electrodes were rinsed with deionized water and immersed into a halide test solution for varying amounts of time. The samples were rinsed with water and characterized electrochemically in a 0.6 mM $\text{Ag}_2\text{SO}_4/0.1\text{M } \text{H}_2\text{SO}_4(\text{aq})$ solution. A standard three-electrode configuration was used to obtain all CVs, and all potentials are quoted relative to silver wire (Ag^+/Ag^0).

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Mid-Membrane Photolabeling of the Transmembrane Domain of Glycophorin A in Phospholipid Vesicles**

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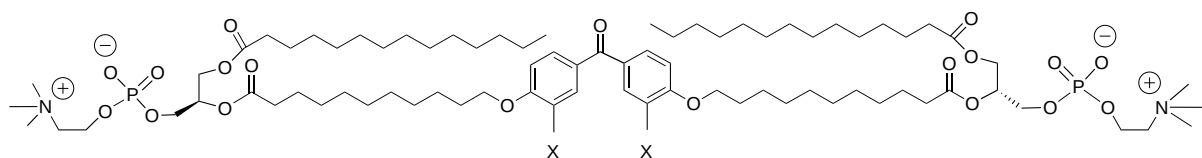
The topography of membrane-bound proteins at atomic resolution is known only in rare cases.^[1] Although the primary amino-acid sequence of glycophorin A (GPA), the major sialoglycoprotein of the human erythrocytes, has been known for more than twenty years and was the first membrane protein sequence elucidated,^[2] a three-dimensional picture of the protein is still missing. We have previously developed the photoactivable membrane probe **1**. This is a phospholipid with two distal, polar heads (a bola-amphiphile) and carries a photosensitive group (benzophenone) in the middle of a transmembrane chain. It is easily incorporated into DMPC (1,2-dimyristoyl-*sn*-glycero-3-phosphocoline) vesicles, where it spans the bilayer at least in the presence of physiological concentrations of cholesterol. We demonstrated recently that the tandem use of the probe **1a** and cholesterol (for its ordering effect) in photolabeling experiments on DMPC vesicles led to a remarkable regioselective functionalization

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1a (X=H), **1b** (X=²H), **1c** (X=³H), **1d** (X=I)

of the ω -1 and ω -2 positions of the surrounding phospholipidic chains and the C-25 position on the side chain of cholesterol.^[3]

Probe **1** has now been used to explore the in situ topography of the transmembrane domain of GPA. GPA consists of a single polypeptide chain of 131 amino acid residues ($M_w \approx 31$ kDa) and has been shown to have a tripartite structure: The extra-cellular N-terminal domain in which 16 amino acids are glycosylated, the hydrophobic transmembrane domain of about 20 amino acids, and the hydrophilic C-terminal domain exposed to the cytosol. Engelman's group showed, by a fluorescence energy-transfer method, that the transmembrane domain of GPA containing residues 62–100/101 (Figure 1), forms a noncovalent dimer in phospholipid



Figure 1. Sequence of the glycoprotein A transmembrane domain and its vicinity: The hydrophobic region^[4,6] is underlined; the residues at the dimer interface are in bold. Stars indicate amino acids photolabeled with probe **1c**.

bilayers.^[4] They also proposed a model for the three-dimensional structure of the dimeric, transmembrane domain of GPA by NMR studies of residues 73–96 of GPA in micelles: a right-handed supercoil of α -helices with a -40° crossing angle.^[5] A dimerization motif, composed of Leu75, Ile76, Gly79, Val80, Gly83, Val84, and Thr87, was identified by mutagenesis studies^[4] and by rotational-resonance NMR studies (Figure 1).^[6]

In this Communication, we describe the analytical process that led us to the identification of the photolabeled amino acids of GPA. The different steps are a) proteoliposome reconstitution, b) photoirradiation, c) trypsin digestion, d) purification of the peptide fraction, and e) Edman degradation. Firstly, proteoliposomes were prepared by a detergent-mediated method^[7] (with *n*-octylglucoside (0.1M) as detergent), from DMPC (61 mol %), DMPS (1, 2-dimyristoyl-*sn*-glycero-3-phosphoserine, 5.0 mol %), cholesterol (33 mol %), radioactive probe **1c** (70 mCi, 0.01 mol %), and GPA (0.2 mol %).^[8] Sucrose density-gradient centrifugation revealed that the proteoliposomes thus obtained comprise only one fraction containing phospholipids (65 mol %), cholesterol (34 mol %), GPA (0.16 mol %), and probe (0.01 mol %). These proteoliposomes were irradiated at 365 nm for 10 min, then treated with trypsin (37 °C, 18 h) to cleave the peptide chain exposed to the exterior of vesicles. Ultracentrifugation of the suspension obtained could separate the precipitate containing the proteoliposome fraction from the aqueous supernatant containing the cleaved small peptide fragments. The precipitate was then extracted twice with cold

ethanol and centrifuged to remove the lipidic components. The remaining peptidic fraction was analyzed by SDS-PAGE (15% acrylamide). Peptide fragment TC (transmembrane fragment plus C-terminal fragment, residues 62–131)^[9] was extracted from the gel and subjected to Edman degradation. The radioactivity associated with the peptide fragment TC corresponds to 5% of the total radioactivity of the starting proteoliposomes. Analysis of the distribution of the radioactivity along the sequence showed that it is restricted to Val80 and Met81 residues (Figure 2). On the other hand, the

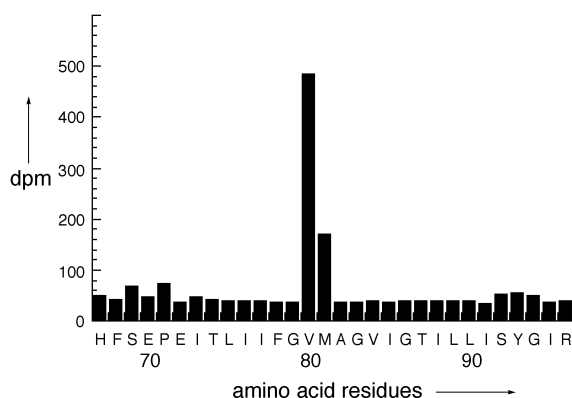


Figure 2. Edman degradation of peptide fragment TC (residues 62–131), and the distribution of radioactivity. The y axis corresponds to the radioactivity (dpm) along the sequence H67 to R96.

orientation of GPA in reconstituted proteoliposomes is very likely to be the same as that in natural erythrocyte membranes, that is, the N-terminal is exposed to the outside of vesicles, since only one dimer of about 18 kDa ($2 \times$ residues 62–131) was detected by Coomassie-blue staining on a SDS-PAGE gel after digestion of the proteoliposomes with proteinase K.^[9]

These results (Figure 2) show that Val80 has been highly regioselectively photolabeled in addition to Met81. Since probe **1b** has been confirmed by a solid-state ²H NMR to be incorporated into DMPC vesicles, in a transmembrane manner, in the presence of 33 mol % of cholesterol^[3] and since the transmembrane domain of GPA (residues 73–95 or 71–99) has been shown by ATR-FTIR measurements to be perpendicular to the bilayer surface in DMPC vesicles by Ruyschaert's^[9] and Smith's^[10] groups, the results show that Val80 and Met81 are localized in the center of the bilayer. Therefore, our results are in a good agreement with the structural features of the transmembrane domain of GPA in membranes, which have been proposed earlier.^[4–6, 9, 10] This represents a marked improvement over the results described earlier. For example, Khorana's group^[11] had tried to use, for

the same goal, phospholipidic probes carrying a photoactivable carbene precursor on the ω -position of the fatty-acid chain. However, most of the crosslinking involved Glu 70, which should be situated at the lipid–water interface in vesicles.^[9] Their results might reflect the extensive disorder of the phospholipidic matrix and of the probe itself above the phase-transition temperature. In our case, the formation of an ordered bilayer structure due to the transmembrane “immobilization”^[3, 12, 13] of the probe and to the concomitant use of cholesterol has led to an excellent selectivity for the photo-labeling on the transmembrane domain of GPA in vesicles.

As judged by Engelman’s three-dimensional model for the dimeric transmembrane domain of GPA, Ala 82 could also be potentially crosslinked by the probe. There could be two possible explanations for the lack of radioactivity associated with Ala 82. Either Phe 78 could generate a steric hindrance as neighbor residue on the preceding α -helical turn or, alternatively, a photochemical reaction had occurred on Ala 82 but a retro-aldol type degradation of the α -coupling product formed might have followed. Such a degradation of α -coupling products of amino acid derivatives, especially in the case of alanine, has been observed by us^[14] and had already been noted by Schöllkopf et al.^[15] In contrast, methionine is functionalized at positions (CH_3 and CH_2) located α to the sulfur atom.^[14, 16] Valine should be attacked at the β -position ($(\text{CH}_3)_2\text{CH}$) in lipid bilayers. Since the radius of the reactive sphere for a benzophenone is estimated to be 3 Å around the carbonyl oxygen atom,^[17] the α -position of valine could not be attacked. Therefore, no such degradation was observed in the case of the valine or methionine adducts.

For the first time, to our knowledge, the center of the transmembrane domain of a protein has been selectively functionalized. Although *photoaffinity-labeling* methods have been successfully employed to determine receptor–ligand binding sites,^[18] there has been no success so far in the site-selective photolabeling of proteins *within* phospholipid bilayers. Despite the limitation cited above for the use of our probe, this method could be useful for the study of transmembrane domains of other proteins.

Experimental Section

Probe **1c** was synthesized from the diiodo precursor **1d**, according to the procedure employed for the synthesis of the dideuterated analogue **1b**^[9] except for the use of $^3\text{H}_2$ in place of $^2\text{H}_2$. For the tritium-labeled compound **1c**, the radiochemical purity was checked by thin-layer chromatography on silica gel and $\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}$ (65/25/4) eluent and by HPLC using a Zorbax NH₂ column (eluent MeCN/MeOH/phosphate buffer pH 4.8 (50/40/10)). The former method showed the purity to be 100%; the latter 98.6%. **1c**: Specific radioactivity 40 Ci mmol^{−1}; ^3H NMR (320 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ (9/1)): δ = 6.90 (single sharp peak); UV/Vis (MeOH): λ_{max} (ϵ) = 200 (30 000), 223 (14 500), 295.5 nm (22 500 M cm^{−1}). **1c** was stored as a stock methanolic solution at -20°C .

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A Direct and Efficient α -Selective Glycosylation Protocol for the Kedarcidin Sugar, L-Mycarose: AgPF₆ as a Remarkable Activator of 2-Deoxythioglycosides**

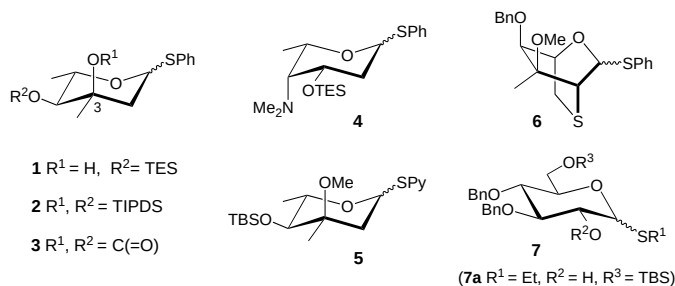
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Without the stereodirecting ability of 2-substituents, strategies to prepare 2-deoxyglycosides selectively in high α - or β -anomeric forms rely heavily on indirect sequences from glycals or latent 2-deoxysugars.^[1–3] As such, these require a subsequent reductive step that would be unsuitable for many

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complex natural products and for any viable total synthesis program. A case in point is that of the kedarcidin chromophore and its α -linked 2,6-dideoxysugars, L-mycarose **1–3** and L-kedarasamine **4** (Scheme 1).^[4–6] In particular, direct and

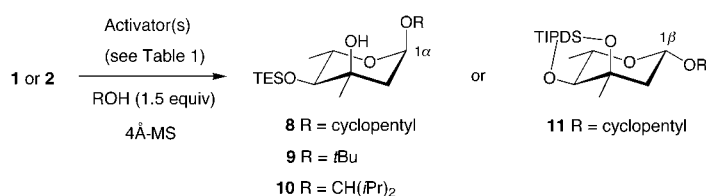


Scheme 1. TES = triethylsilyl, TIPDS = 1,1,3,3-tetraisopropylidisiloxane-1,3-diyl, Bn = benzyl, TBS = *tert*-butyldimethylsilyl, Py = 2-pyridyl.

efficient α -selective methods for *allo*-configured systems **1–3** and **5** are especially difficult to realize.^[3] For example, to overcome the lack of success in the α -glycosylation of erythromycin A, Toshima, Tatsuta and co-workers developed the masked 2,6-anhydrothiopyranoside **6** of L-cladinose.^[3c,d] As notable exceptions, the groups of Martin and Nicolaou have reported direct procedures that are partially α -selective in CH_3CN ; namely, *N*-bromosuccinamide activation of **3** and $Cu(OTf)_2/CuO$ ($Tf = triflate = OSO_2CF_3$) activation of **5**.^[3e,g] Herein we describe a direct, potent, and mild protocol to efficiently generate α -L-mycarosides from **1** or **2** by using $AgPF_6$, which is exemplified by the α -mycosylation of an advanced kedarcidin substructure **14**. Although the present method is applicable to other 2-deoxy systems, such as the synthesis of α -L-kedarasaminides from **4**, normal 2-oxythioglycosides **7** remain inert to $AgPF_6$ and can be used as acceptors armed with strategic anomeric linkages.

Based on previous work, stable α - and β -thioglycosides **1, 2**, and **4** were readily prepared in anomerically pure form.^[5b] Preliminary model studies on **2** and literature precedent revealed that any protection of a 3-hydroxy group in a 2-deoxy-*allo*-pyranoside apparently confers enough *A* strain to suppress the normally preferred kinetic mode of α -anomeric (axial) attack.^[1–3] As a consequence, various activation methods that could tolerate the unprotected tertiary 3-OH in thioglycoside **1** were investigated.^[7]

Although the thiophilic activators $PhSOTf$ and $PhSeOTf$ gave encouraging results in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP),^[7a,b] it was found that $Me_2S^+ - OTf$ (DMTST) and $Me_2S^+ - SMe - BF_4$ (DMTSB) generated **8** from **1** in acceptable yields and α -selectivity (Scheme 2, Table 1).^[7c] Although changes in solvent at various temperatures gave similar stereochemical results, there was a distinct difference in the α/β anomer ratio between the two reagent systems (Table 1, entries 1 and 2). Based on this observation and to make the reaction more amenable to low temperatures for DMTSB (Table 1, entry 2), the effect of adding thiophilic additives with different counteranions was investigated. Remarkably, the addition of silver salts not only gave acceptable reaction times even at $-80^\circ C$, but gave a stereochemical outcome for DMTSB similar to that found for



Scheme 2. Complementary and direct α - and β -glycosylation protocols for L-mycarose: Realization of α -selectivity by using the partially protected system **1**. 4 Å MS = molecular sieves (4 Å).

Table 1. Stereoselective glycosylation of cyclopentanol with phenyl thioglycosides **1** or **2** (Scheme 2).^[a]

Entry	Activator(s)	Solvent	$T [^\circ C]$	$t [h]$	Yield [%]	α/β ratio ^[b]
1 ^[c]	DMTST	Et_2O	0	2	71	1.3
2 ^[c]	DMTSB	Et_2O	0 ^[d]	4	84	2.5
3	DMTST/ $AgOTf$	Et_2O	-80	15	61	1.5
4	DMTSB/ $AgOTf$	Et_2O	-80	15	64	1.5
5	$AgOTf$	Et_2O	-28	7	81	2.0
6	$AgBF_4$	Et_2O	-40	7.5	85	2.1
7	$AgPF_6$	Et_2O	0 ^[e]	1.5	85	4.5
8	$AgSbF_6$	Et_2O ^[f]	0	2.5	71	4.8
9	$AgPF_6$	CH_2Cl_2	0	0.5	88	7.7
10	$AgPF_6$	CH_2Cl_2	-60	13	79	7.7
11	β -1/ $AgPF_6$	CH_2Cl_2	0	2	88	14.0
12	α -2/ $AgPF_6$	CH_2Cl_2	0	0.5	87	11 (3.9)
13	β -2/ $AgPF_6$	CH_2Cl_2	0	2	83	11 (6.7)
14 ^[g]	2/ Cp_2HfF_2	CH_2Cl_2 ^[h]	-50	1	82	11 (β -only)

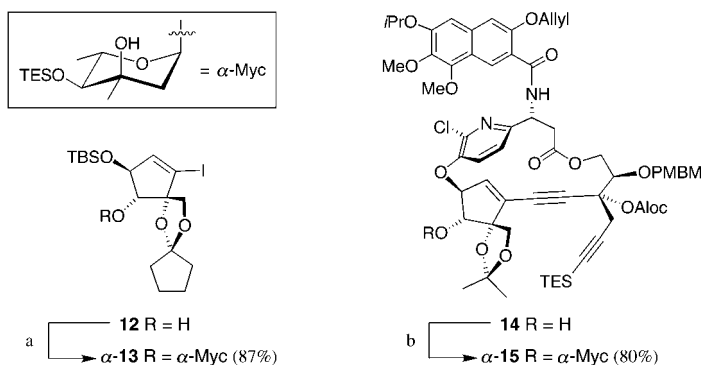
[a] Except for entries 11–14, reactions were performed using α -**1** with the activating system (3–4 equiv) and DTBMP (4.0 equiv); yields are reported relative to **8**; see text for abbreviations. [b] Determined on the crude mixture by 500 MHz ^1H NMR integration of anomeric signals. [c] At $-28^\circ C$: Et_2O , CH_2Cl_2 , and mixtures with CH_3CN , gave $\alpha/\beta \approx 1.4$ (for DMTST) and $\alpha/\beta \approx 2.5$ (for DMTSB). [d] Poor conversion below $0^\circ C$. [e] 90% complete at $-60^\circ C$ after 13 h, $\alpha/\beta = 4.8$. [f] In CH_2Cl_2 , $\alpha/\beta = 5.6$. [g] Glycosyl fluoride ($\alpha/\beta = 1:1.9$) derived from **2** ($\alpha/\beta = 1:5.4$) and $Cp_2HfCl_2/AgClO_4$ (1:2) used.^[2c, 8] [h] Best in THF, $\alpha/\beta = 1:1.7$.

DMTST (Table 1, entries 3 and 4). Indeed, the sole use of a silver salt was sufficient for a rapid reaction, and $AgPF_6$ gave α/β ratios approaching 8:1 in favor of the α -anomer (Table 1, entries 9 and 10). Although the temperature did not greatly influence the stereochemical outcome, a change of solvent from Et_2O to CH_2Cl_2 with $AgPF_6$ gave an improvement in both the reaction rate and the α/β ratio (Table 1, cf. entries 7 to 10).

Additional experiments revealed that a superior α -selectivity resulted when the β -thioglycoside of **1** was used (Table 1, cf. entries 9 and 11) and, remarkably, both anomeric forms of the bulky thioglycoside **2** with cyclopentanol gave an α -rich mixture of **11** when treated with $AgPF_6$ (Table 1, entries 12 and 13). These latter results were surprising since extensive studies with fluorophilic complexes and a glycosyl fluoride derived from **2** only ever gave β -selectivity, for example $[Cp_2HfCl_2]/AgClO_4$ gave β -**11** exclusively and complements the α -selective $AgPF_6$ method for this sugar-type (Table 1, cf. entries 11 and 14).^[2c, 8] Control experiments further revealed that α -**1** and α -**2** reacted more quickly with $AgPF_6$ than their β -counterparts. Also, in the absence of alcohol, pure α -**2** rapidly epimerized to form a β -rich mixture ($\alpha/\beta = 1:10$, $0^\circ C$, 2 h), whereas β -**2** retained its anomeric integrity. Collectively, these findings suggest that the activa-

tion of α -1 and α -2 involves the intermediacy of an oxocarbenium salt and that the α -stereoselectivity conceivably results from an anionic species adopting a pseudo-equatorial position. For β -forms, the reversible formation of a less reactive AgPF_6 -thiosugar complex that directly undergoes $\text{S}_{\text{N}}2$ displacement can be envisaged.

At this juncture it was imperative to determine if this method could be applied to more demanding glycosyl acceptors (Scheme 2, 3). As such, **12** and **14** were assembled through



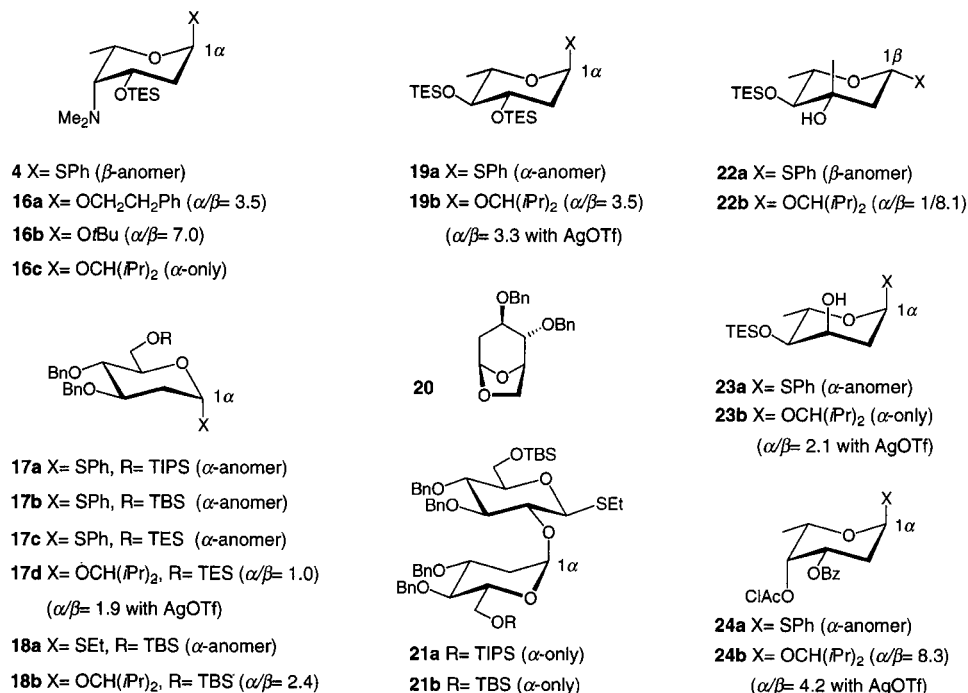
Scheme 3. Direct and efficient α -mycoosylation of hindered kedarcidin subunits by using $\text{AgPF}_6/\text{DTBMP}$ in CH_2Cl_2 at 0°C . a) α -1 (1.8 equiv), 1.5 h; b) β -1, (6.0 equiv), 6 h (97% based on recovered **14**). PMBM = *p*-methoxybenzyloxymethyl, Alloc = allyloxycarbonyl.

the elaboration of recent synthetic work on the kedarcidin chromophore.^[5a] Gratifyingly, the application of α -1/ $\text{AgPF}_6/\text{DTBMP}$ to *t*BuOH, *i*Pr₂CHOH, and **12**, generated the respective α -mycarosides **9**, **10**, and **13** exclusively in excellent yields (87–99%). To further confirm the α -selectivity induced by AgPF_6 , the reactions that gave **9** and **10** were repeated with AgOTf , and significant amounts of β -products resulted ($\alpha/\beta \approx 2.5$). Most importantly, the efficiency of $\text{AgPF}_6/\text{DTBMP}$ was clearly demonstrated in the construction of the formidable chromophoric subunit α -15 from **14** (Scheme 3).^[9] In this case, it was vital to use the less reactive β -anomer of **1**, since with complex systems similar to **14**, a large excess of α -1 and AgPF_6 tended to give products with two sugar units attached in 10–15% yield. In addition, as long as the terminal acetylene in **14** was protected with a TES group, the possibility of undesired side reactions due to silver complexation was not a problem.^[10]

The present glycosylation conditions (Table 1, entry 9) were then applied to other 2-deoxy systems, especially to the L-kedarcidin derivative **4** and to the *ribo*-configured (*allo*-like) L-digitoxose derivative **23** (Scheme 4).^[3b] In brief, all phenyl and ethyl 2-deoxythioglyco-

sides tested so far with $\text{AgPF}_6/\text{DTBMP}$ (3–6 equiv) and an alcohol acceptor (2–3 equiv) afforded their corresponding 2-deoxyglycoside **16**–**24** in 75–99% yields, with low to high α -selectivity (except for olivomycarose derivative **22**) at 0°C in CH_2Cl_2 over 0.5–2 h. In comparison, reactions performed with AgOTf remained 15–60% incomplete, even with excess reagents (8–20 equiv) at room temperature over 5 h, and typically gave lower α -selectivity. Furthermore, free amino and hydroxy groups in the donor system are well tolerated (cf. **4**, **22**, and **23**, Scheme 4) and the relatively labile OTES and chloroacetate (ClAc) groups are stable to these conditions (cf. **17c**, **d**, **19**, **22**–**24**, Scheme 4). However, in an attempt to conjugate **17c** with β -7a (Scheme 1) using AgPF_6 , the cyclized product **20** (Scheme 4) was formed (73%). Notably, β -7a was fully recovered in this case and normal 2-oxythioglycosides **7** ($\text{R}^1 = \text{Ph}$ or Et ; R^2 , $\text{R}^3 = \text{Bn}$, Ac , TBS) in general are unreactive to these conditions, even with a large excess of $\text{AgPF}_6/\text{DTBMP}$ (50 equiv) at room temperature over 48 h. As such, interesting disaccharides that bear dormant sulfur weaponry for future glycosylation steps can be readily accessed, for example, the reaction of β -7a with α -17a, **b** exclusively gave α -21a, **b** (84–86%).^[11]

In conclusion, while making significant headway towards assembling the kedarcidin chromophore,^[5] we have established that $\text{AgPF}_6/\text{DTBMP}$ is an exceptionally mild activating system for simple 2-deoxythioglycosides that are stable to storage and more readily prepared than their customized *S*-heteroaryl counterparts or *S*-carbodithioates.^[3g, 7d, 12] Within the complex realms of natural product and carbohydrate synthesis, the potential of this and related Ag^I -based systems to sensitive and sterically hindered acceptors should thus help inspire new strategies with which to construct advanced 2-deoxyglycosides in a straightforward, direct, and stereoselective manner.^[1, 3b,f]



Scheme 4. Expedient formation of 2-deoxyglycosides **16**–**24** of $\text{PhCH}_2\text{CH}_2\text{OH}$, *t*BuOH, *i*Pr₂CHOH, or **7a**, by using $\text{AgPF}_6/\text{DTBMP}$ (see text). ClAc = chloroacetyl, Bz = Benzoyl.

Experimental Section

General protocol: The 2-deoxythioglycoside (0.1 mmol), alcohol (1.5 equiv), and DTBMP (4.5 equiv) were dissolved in CH_2Cl_2 (1.0 mL) under argon, using light-protected glassware. After the mixture had been stirred for 1.5 h at 23 °C over molecular sieves (4 Å, <5 microns, freshly activated), powdered AgPF_6 (3–4 equiv) was added at 0 °C. When the reaction was complete (0.5–2 h), pyridine (50 equiv) was added, and the mixture was stirred for a further 0.5 h. Filtration (celite pad, diethyl ether/*n*-hexane (1:4)), concentration, and chromatographic purification provided the 2-deoxyglycoside.

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H₂O₂-Dependent Fe-Catalyzed Oxidations: Control of the Active Species**

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Jean-Baptiste Galey, Colette Lebrun, and
Jacques Pécaut

In memory of Olivier Kahn

The reaction of ferrous ion with hydroperoxides has been investigated for more than a century (Fenton chemistry), and yet the mechanism has still not been satisfactorily rationalized. The nature of the reactive species has always been a matter of debate, oscillating between hydroxyl or alkoxyl

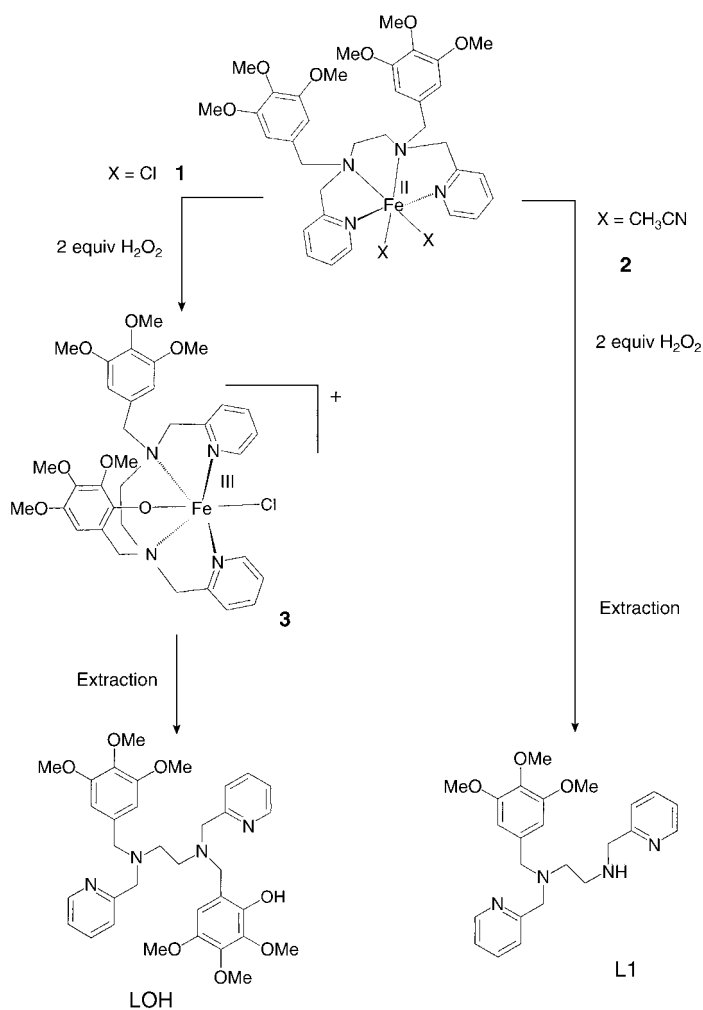
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radicals and an oxene species.^[1,2] Moreover, the discovery that non-heme-iron proteins can oxidize inert substrates (e.g., alkanes) selectively has stimulated chemists to reinvestigate the reaction of non-heme-iron complexes with dioxygen- and oxygen-derived oxidants.^[3] In fact, dinuclear, methane monooxygenase,^[4] and mononuclear non-heme-iron enzymes such as isopenicillin N synthase, 2-oxo-glutarate-dependent enzymes, and pterin-dependent phenylalanine, tyrosine, tryptophan hydroxylases are proposed to carry out a two-electron oxidation via an Fe^{IV}-oxo moiety.^[5] Herein, we report on the oxidation mechanism by using iron complexes of the ligand *N,N'*-bis(pyridin-2-ylmethyl)-*N,N'*-bis(3,4,5-trimethoxybenzyl)ethane-1,2-diamine (L) as a substrate.^[6] This ligand displays several potential oxidation sites, in particular the methylene groups and phenyl rings from benzylic moieties; the latter are known to be very reactive towards hydroxyl radicals, leading to the formation of phenol.^[7] Herein we compare the catalytic properties of two complexes, [Fe^{II}LCl₂]·0.25 H₂O (**1**·0.25 H₂O) and [Fe^{II}L(CH₃CN)₂(ClO₄)₂]·3 H₂O (**2**(ClO₄)₂·3 H₂O), during oxidation of ligand L (Scheme 1) and of various substrates by H₂O₂ in acetonitrile. With such probes we demonstrate that complex **1** behaves as a typical Fenton reagent, whereas complex **2** functions through metal-based mechanisms. This

shows that for this class of iron complexes the reactivity can be tuned by modifying the simple monodentate ligand.

The synthesis of complexes **1** and **2** started with mixing equimolar amounts of FeCl₂·4H₂O or Fe(ClO₄)₂·6H₂O, respectively, and the ligand L in CH₃OH under argon. Addition of diethyl ether to the CH₃OH solution afforded in both cases a yellow powder. Slow diffusion of diethyl ether into a solution of these powders in acetonitrile afforded crystals suitable for X-ray structure analysis (Figure 1).^[8] The crystal structures of **1**·CH₃CN and **2**(PF₆)₂·2.5 CH₃CN·0.25 CH₃OH·0.5 H₂O reveal that in each case the Fe center is octahedrally coordinated; the coordination differs with respect to the nature of the two ligands that occupy the two *cis*-positioned open sites of the Fe^{II} coordination sphere: in compound **1** they are filled by chloride ions, whereas in **2** they are filled by acetonitrile solvent molecules. This difference confers a different spin state to the ferrous ion in the solid state only (shown by the longer Fe–N distances in **1** than in **2**). Complexes **1** and **2** displayed significantly different



Scheme 1. Ligand oxidation of complexes **1** and **2** to give LOH and L1, respectively.

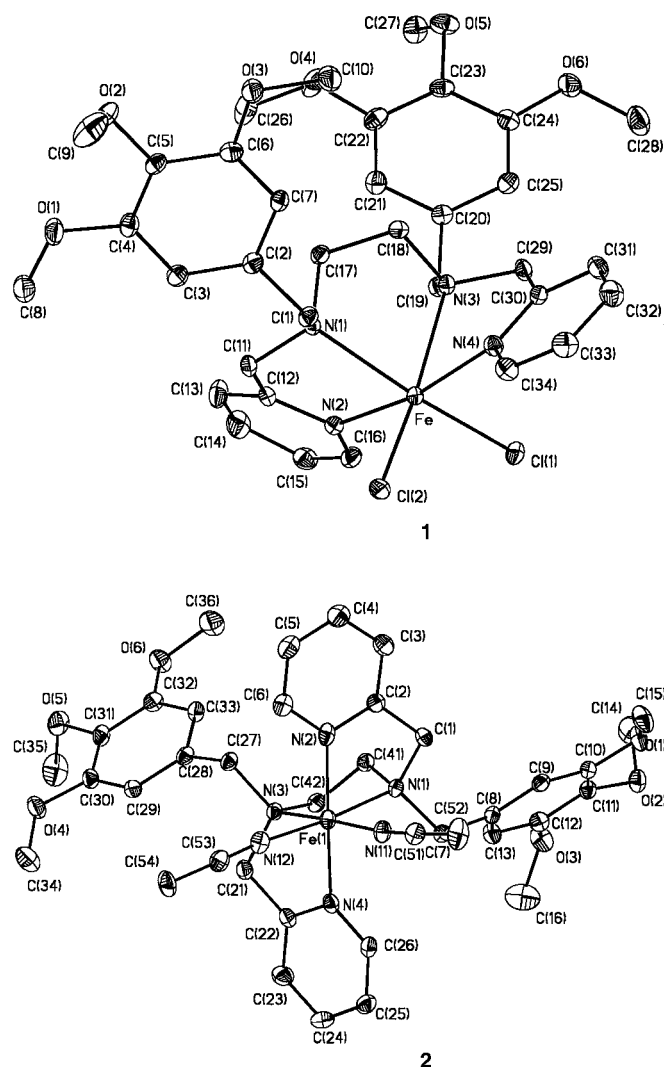


Figure 1. ORTEP representation of complexes **1** and **2**. Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å]: for **1**: Fe–N(1) 2.3272(7), Fe–N(2) 2.2120(6), Fe–N(3) 2.3012(6), Fe–N(4) 2.2228(6); for **2**: Fe(1)–N(11) 1.939(4), Fe(1)–N(12) 1.942(4), Fe(1)–N(2) 1.986(4), Fe(1)–N(4) 1.988(4), Fe(1)–N(1) 2.055(4), Fe(1)–N(3) 2.061(4).

resonance signals in their ^1H NMR spectra in acetonitrile between $\delta = 160$ and -20 (data not shown).

When an excess of H_2O_2 was added to a solution of complex **1** (1 mM) in acetonitrile under argon, the solution immediately turned blue. Titration studies showed that only two equivalents of hydrogen peroxide were required to achieve maximal intensity of a new transition at 740 nm. The new species was characterized as a mononuclear phenolatoiron(III) complex $[\text{Fe}^{\text{III}}(\text{LO})\text{Cl}_2]$ (Scheme 1) based on the following spectroscopic signatures: 1) the transition at 740 nm was assigned to a charge-transfer band from an oxygen atom of the phenolato ligand to an iron(III) center;^[9] 2) the positive-ion mode ESI mass spectrum of the resulting solution displayed only one molecular peak at m/z 708 (100%) attributed to $[\text{Fe}(\text{L}-\text{H})\text{Cl} + \text{O}]^+$ whose isotopic pattern was in agreement with the theoretical one; 3) an isotropic signal was observed at $g = 4.3$ in the EPR spectrum of the resulting solution.

The oxidized ligand was then extracted and characterized^[10] by ESI-MS and ^1H NMR analysis as *N*-(2-hydroxy-3,4,5-trimethoxybenzyl)-*N,N'*-bis(pyridin-2-ylmethyl)-*N'*-(3,4,5-trimethoxybenzyl)ethane-1,2-diamine which results from the hydroxylation at the *ortho* position of one phenyl ring of the ligand.^[11] HPLC titration showed that more than 70(± 10)% of the ligand **L** had been transformed into LOH and only 6(± 5)% of the starting ligand was found unconverted.^[12] Mass spectrometric analysis of the modified ligand LOH obtained when $\text{H}_2^{18}\text{O}_2$ was used as an oxidant established that the oxygen atom incorporated came exclusively from the oxidant. Control experiments in the presence of H_2^{16}O in the $\text{H}_2^{18}\text{O}_2$ -dependent reaction did not alter the yield of ^{18}O -atom incorporation. Aromatic hydroxylation of the ligand in iron complexes has been previously reported.^[6, 13]

In contrast, addition of H_2O_2 to complex **2** (ClO_4)₂ under the same conditions as for **1** did not result in any intense color change.^[14] Moreover, extraction of the organic material from the reaction mixture and analysis by HPLC led to the recovery of 65(± 10)% of the unconverted ligand **L** and the isolation of a new modified ligand **L1** in 14(± 5)% yield (see Scheme 1). **L1** was characterized by ESI-MS and ^1H NMR analysis^[15, 16] as *N,N'*-bis(pyridin-2-ylmethyl)-*N*-(3,4,5-trimethoxybenzyl)ethane-1,2-diamine which resulted from an *N*-dealkylation of the **L** ligand. No evidence for the formation of LOH in this reaction was obtained. Clearly, the nature of the two monodentate ligands (Cl vs. CH_3CN) influenced the selectivity of the ligand oxidation, suggesting the participation of different oxidative species.

To distinguish between these reactive species, the catalytic properties of the **1**/ H_2O_2 or **2**/ H_2O_2 combination towards external substrates was studied.^[17] Only **2** led to catalytic and stereoselective alkane hydroxylation under anaerobic conditions. For example, the reaction of *cis*-1,2-dimethylcyclohexane with **2**/ H_2O_2 led to the catalytic formation of *cis*-1,2-dimethylcyclohexanol and *trans*-1,2-dimethylcyclohexanol in a 10:1 ratio (yield based on the oxidant 20%), whereas the analogous reaction with the **1**/ H_2O_2 combination led to an equimolar mixture of *cis*- and *trans*-1,2-dimethylcyclohexanol (yield 7%). Furthermore, catalytic oxidation of cyclohexane to give cyclohexanol and only minor amounts of cyclohex-

anone (yield based on the oxidant 38%; alcohol/ketone 8/1) occurred only with complex **2**, whereas equimolar amounts of alcohol and ketone were detected with complex **1** as the catalyst (yield based on the oxidant 6%). The origin of the oxygen atom incorporated into cyclohexane has been determined in both cases.^[18] When 10 equivalents of $\text{H}_2^{18}\text{O}_2$ were mixed with **2** in the presence of 1000 equivalents of H_2^{16}O , 47(± 3)% of the cyclohexanol was ^{18}O -labeled. This was confirmed when ^{18}O -labeled water and unlabeled H_2O_2 were used. In contrast, with complex **1** and $\text{H}_2^{18}\text{O}_2$, cyclohexanol was fully labeled with the oxygen atom from the oxidant; no exchange with water was observed. Finally, only complex **2** was capable of epoxidizing cyclooctene (30% yield based on the oxidant) and cyclohexene (20% yield based on the oxidant) substrates.^[19] Notably, in the case of cyclohexene, allylic oxidation products were the major products regardless of the catalyst (only 2-cyclohexen-1-ol was formed; yield 10%).

All these data taken together imply two different oxidative pathways depending upon the catalyst structure. In the case of complex **1**, the quasi-quantitative hydroxylation of the pendant phenyl ring of the ligand, the origin of the oxygen atom from the oxidant, the poor (stereo)selectivity during alkane oxidation, and the lack of epoxidation strongly suggest that freely diffusing $\text{OH}^\bullet$ is the active species.^[20, 21] In contrast, in the case of complex **2**, the high stereoselectivity, the solvent oxygen atom exchange, the oxidation of the closest C–H bond of the ligand (the methylene group of the benzyl ring), and the reasonable yield of epoxides can be interpreted with the involvement of an iron–oxo complex as an active species, allowing a better control of the substrate radicals (“caged radicals”) by the metal center. The participation of free hydroxyl radicals when catalyst **2** was used is thus unlikely. The presence of products labeled with oxygen atoms from both water and the oxidant has already been observed in oxidations dependent on heme- and non-heme-iron complexes and has been explained by a postulated “oxo–hydroxo tautomerism” of the Fe^{IV} or $\text{Fe}^{\text{V}}=\text{O}$ intermediate.^[22–25]

One possible explanation for the difference between **1** and **2** is the presence of labile sites only in **2**, which thus allow the binding of H_2O_2 to the metal center. Complex **1** would thus react with H_2O_2 through an outer-sphere electron transfer resulting in formation of $\text{OH}^\bullet$. In contrast, with complex **2** an iron–peroxo species, similar to peroxo complexes previously observed during H_2O_2 -dependent reactions, can be transiently formed as a precursor for a metal-based oxidative species.^[26] The nature of this species remains to be established. We favor a homolytic cleavage of the $\text{FeO}-\text{OH}$ bond, leading to a caged $[\text{Fe}^{\text{IV}}=\text{O} \text{ OH}^\bullet]$ radical pair.

This work further supports the notion that high-valent iron–oxo species (and not only $\text{OH}^\bullet$ radicals) can be generated and used as active species in non-heme-iron catalysis. Furthermore, it shows that the balance between different catalytic pathways for the oxidation ($\text{OH}^\bullet$ vs. metal-based oxidant) can be tuned through the manipulation of the coordination sphere of the ferrous ion.

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- [10] The resulting solution was concentrated and diluted in water in the presence of excess dithionite and bathophenanthroline. The organic material was extracted from the solution by using dichloromethane and chloroform.
- [11] Comparisons between ¹H and ¹³C NMR spectra of **L** and **LOH** allowed us to unambiguously attribute the inserted oxygen position. In fact, the signal at δ = 6.63 corresponding to the *o*-H for **L** is replaced by two signals at δ = 6.63 and 6.42 in a 2:1 ratio for **LOH**. A similar trend is observed in the ¹³C NMR spectrum (for the *o*-C of the phenyl ring signals appear at δ = 108.5 and 105.5 for **LOH**, but only at δ = 105.0 for **L**). ESI-MS for **LOH** (CH₂Cl₂; positive-ion mode): *m/z*: 619 (100%) for [LOH + H⁺].
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- [14] The reaction mixture contains both mononuclear Fe^{II} and Fe^{III} **L** and **L1** complexes.
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- [16] Accordingly, the pendant product of the N-dealkylation of the ligand, 3,4,5-trimethoxybenzaldehyde, has been quantitatively detected.
- [17] Experimental conditions: complex/alkane/H₂O₂ 1/1100/10 in acetonitrile inside a glove box (dioxxygen content less than 1 ppm) using syringe pump conditions; delivering time = 30 min [complex] = 0.7 mM.
- [18] The isotope ratio in cyclohexanol has been analyzed by GC/MS on a reaction mixture directly after reaction. Cyclohexanol was not labeled in the presence of ¹⁸O water under standard conditions.
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A Route to a Germanium–Carbon Triple Bond: First Chemical Evidence for a Germyne**

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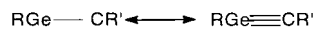
Since the isolation of the first disilene, a compound containing a silicon–silicon double bond, in 1981,^[1] many stable compounds with a double bond involving the Group 14 elements Si, Ge, and Sn have been synthesized.^[2] In contrast, compounds containing a triple bond to a Group 14 element other than C remained unknown. Power^[3] described recently a lead analogue of an alkyne (ArPbPbAr) but more consistent with a diplumbylene form. However, some compounds with triple bonds to Si were identified by spectroscopy or by

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various other methods.^[4] Germaisonocyanides $\text{:Ge}\equiv\text{NR}$ have only been detected by photoelectron spectroscopy,^[5] whereas in coordination chemistry, stable transition metal germylyne complexes have been reported and structurally characterized since 1996.^[6] No triple bond to tin has yet been described.

Besides the difficulty in isolating such a triply bonded compound and the possibility that more stable isomers exist, the major obstacle remains to find a suitable synthetic method. We considered a potential route to germynes $\text{RGe}\equiv\text{CR}'$ from a germylene–carbene structure (Scheme 1).

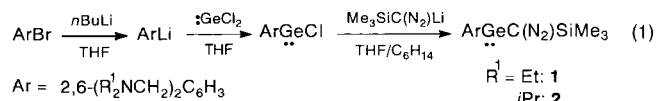


Scheme 1. Resonance forms: germylene–carbene and germyne.

Coupling reactions between germylenes (or stannylene) and carbenes that provide convenient access to $\text{Ge}-\text{C}$ and $\text{Sn}-\text{C}$ double bonds^[7,8] prompted us to extend such a methodology to the formation of a germanium–carbon triple bond from a σ -bonded germylene–carbene compound. Generation of a carbene moiety adjacent to a Group 14 element bearing both a lone pair and a vacant p orbital^[9] appears to be an attractive method for the synthesis of a triply bonded metal–carbon species. Diazogermynes $\text{RGeC}(\text{N}_2)\text{R}'$ may be convenient precursors for the formation of such a unit by photolysis or thermolysis. We describe here the synthesis and the structure of diazogermynes $\text{ArGeC}(\text{N}_2)\text{SiMe}_3$ and an initial study of their photochemical behavior.

The 2,6-bis[(dialkylamino)methyl]phenyl groups $(\text{R}_2\text{NCH}_2)_2\text{-C}_6\text{H}_3$ (Ar) are suitable ligands because of their steric bulk and, in particular, their stabilizing effect due to intramolecular coordination of the nitrogen lone pair to empty orbitals on the metal atom. The use of this kind of ligand has allowed the preparation of sensitive derivatives of main group elements, such as gallium and indium halides ($\text{R}^1 = \text{Me}, \text{Et}$)^[10a-c] as well as a chlorostannylene ($\text{R}^1 = \text{Me}$).^[10d]

The diazogermynes were obtained in good yields by one-pot synthesis [Eq. (1)]. Compounds **1** and **2** are readily soluble



in hydrocarbon and ether solvents and have been fully characterized. Whereas **1** is a yellow, viscous oil, **2** is crystalline, and single crystals suitable for an X-ray structure determination were grown from pentane at -20°C . The structure analysis^[11] showed **2** to be monomeric in the solid state (Figure 1).

The Ar ligand is bound to germanium in a bidentate fashion with a σ bond to the *ipso*-carbon atom C5 and intramolecular coordination of the N atom of a CH_2NiPr_2 side chain. The $\text{Ge1}-\text{N3}$ distance of 2.35(9) Å is, as expected, longer than the a normal $\text{Ge}-\text{N}$ σ bond (1.92 Å^[12a]) but much shorter than the sum of the van der Waals radii (3.74 Å^[12b]). The $\text{Ge}-\text{N4}$ distance (3.05(3) Å) indicates a weak interaction between the N atom of the other side chain and the metal atom. The coordination sphere of germanium is completed by the $\text{Ge1}-\text{C1}$ bond, which is oriented almost orthogonal (96.8°)

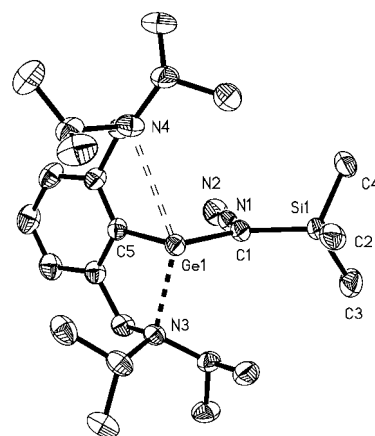
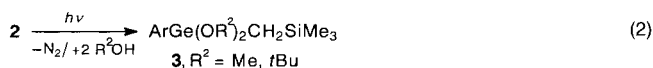


Figure 1. Molecular structure of **2** in the solid state. Selected distances [Å] and angles $^\circ$: $\text{Ge1}-\text{C5}$ 2.006(5), $\text{Ge1}-\text{C1}$ 2.02(1), $\text{Si1}-\text{C1}$ 1.85(8), $\text{Ge1}-\text{N3}$ 2.35(9), $\text{Ge1}-\text{N4}$ 3.05(3), $\text{C1}-\text{N1}$ 1.298(2), $\text{N1}-\text{N2}$ 1.146(2); $\text{C5}-\text{Ge1}-\text{C1}$ $96.84(7)$, $\text{C5}-\text{Ge1}-\text{N3}$ $80.46(6)$, $\text{C1}-\text{Ge1}-\text{N3}$ $98.94(6)$, $\text{N1}-\text{C1}-\text{Si1}$ $115.55(12)$, $\text{Ge1}-\text{C1}-\text{Si1}$ $128.0(8)$, $\text{Ge1}-\text{C1}-\text{N1}$ $116.33(11)$, $\text{N2}-\text{N1}-\text{C1}$ $178.02(10)$.

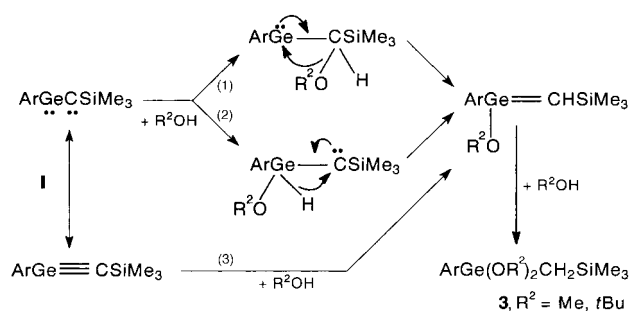
to the plane of the aryl ligand. The $\text{Ge1}-\text{C1}$ (2.02(1) Å) and $\text{C1}-\text{Si1}$ (1.85(8) Å) bond lengths are close to the normal values for σ bonds of 1.99 and 1.94 Å, respectively.^[12a] The $\text{Ge1}-\text{C1}-\text{Si1}$ angle of $128.0(8)^\circ$ is consistent with sp^2 hybridization of carbon atom C1 and a repulsive steric interaction between germanium and the SiMe_3 group.

When a solution of **2** in toluene was irradiated at -50°C and $\lambda = 300\text{ nm}$ in the absence of a trapping agent, we observed evolution of nitrogen and formation of polymeric materials. Elemental analyses of these polymers are compatible with a formula such as $(\text{ArGeCSiMe}_3)_n$. When the same irradiation was carried out in the presence of an alcohol as a trapping agent, **3** was obtained in nearly quantitative yield for $\text{R}^2 = \text{tBu}$ and in 40% yield for $\text{R}^2 = \text{Me}$ [Eq. (2)]. The



formation of **3** from the germylene–carbene species $\text{ArGe}=\text{C}=\text{SiMe}_3$ (**I**) formed by photolysis of **2** can be explained by three possible mechanisms (Scheme 2): **I** can react as a carbene (1), as a germylene (2), or as a germyne (3). All processes involve the transient formation of germene $\text{ArGe(OR}^2\text{)=CHSiMe}_3$, but routes 1 and 2 require rearrangement reactions.

Mechanism 1 can be excluded since **I** does not behave as a carbene; for example, it does not react with dienes such as 2,3-dimethylbutadiene, which is well known to react with



Scheme 2. Possible mechanisms of the trapping reaction (2).

carbenes.^[13] Moreover, kinetic studies have shown that the reactivity of alcohols towards carbenes is proportional to their acidity and that the relative reactivity of tertiary alcohols such as *t*BuOH is low.^[14] As diazogermylene **2** does not react with *t*BuOH at room temperature or with MeOH at low temperature, it does not behave as a germylene, and this rules out mechanism 2. The lack of typical carbene and germylene reactivity of **1** suggests that it is reasonable to postulate mechanism 3, in which the germyne is trapped by two equivalents of alcohol.

In conclusion, diazogermylenes, in which a carbenoid species is adjacent to a Group 14 atom bearing both a lone pair and vacant orbitals, are promising precursors to germanium–carbon triple bonds. Our results, which constitute the first chemical evidence for a germyne, contrast with *ab initio* quantum mechanical calculations of Stogner and Grev on the parent molecule HGe≡CH, which indicated that the germynylidene isomer :Ge=CH₂ is 7 kcal mol^{−1} more stable than *trans*-bent germyne, and 43 kcal mol^{−1} more stable than the linear germyne.^[15] However, our results are in accordance with the work of Apeloig and Karni in the field of silicon chemistry, who predicted that bulky substituents are expected to destabilize the vinylidene structure relative to the triple bond.^[16]

Experimental Section

All experiments were performed under a dry and oxygen-free argon atmosphere. Solvents were dried by appropriate methods. Melting points were determined in capillaries sealed under argon and are not corrected.

1: *n*-Butyllithium (4.2 mL, 1.6 M in hexane) was added dropwise to ArBr (2.0 g, 6.1 mmol) in THF (15 mL) at −78 °C, and the mixture was stirred for 20 min. A solution of GeCl₂·dioxane (1.4 g, 6.1 mmol) in THF (15 mL) was then added at the same temperature, and the reaction mixture was stirred for 30 min at room temperature. A solution of lithiotrimethylsilyldiazomethane (6.1 mmol) prepared from a solution of trimethylsilyldiazomethane (3.05 mL, 2 M in hexane) and *n*BuLi (4.2 mL, 1.6 M in hexane) in THF (15 mL) was added dropwise to the above mixture at −78 °C, and the solution was stirred at room temperature for 30 min. Solvents were removed in vacuum, and the residue was dissolved in pentane. The mixture was filtered, the solvents evaporated, and **1** was obtained as viscous oil (1.98 g, 75 % yield). ¹H NMR (400.1 MHz, C₇D₈, TMS): δ = 0.55 (s, 9H, Me₃Si), 1.11 (t, ³J(H,H) = 6.7 Hz, 12H, CH₂CH₃), 2.83 (q, ³J(H,H) = 6.7 Hz, 8H, CH₂CH₃), 3.63, 3.75 (AB system, ²J(H,H) = 14.2 Hz, 4H, CH₂), 7.10–7.30 (m, 3H); ¹³C NMR (100.6 MHz, C₇D₈, TMS): δ = 0.40 (¹J(¹³C,²⁹Si) = 26.6 Hz, CH₃Si), 9.84 (CH₂CH₃), 24.49 (CN₂), 45.31 (CH₂CH₃), 59.77 (CH₂), 124.54 (*m*-C), 127.69 (*p*-C), 145.21 (*o*-C), 156.85 (*ipso*-C); ¹⁴N NMR (28.9 MHz, C₇D₈, MeNO₂): δ = −110 (¹⁴N_α), ¹⁴N_β signal too weak to be observed; ²⁹Si NMR (39.8 MHz, C₇D₈, TMS): δ = −0.98 (Me₃Si); EI-MS (70 eV): *m/z* (%): 434 (21) [*M*⁺], 377 (2) [*M*⁺ − Et − N₂], 321 (100) [ArGe], 291 (42) [ArGe − 2Me], 220 (52) [ArGe − NEt₂ − Et], 177 (35) [ArGe − 2NEt₂]; IR (C₆D₆): ν̄ = 1994 cm^{−1} (CN₂).

2: The same procedure as for **1** was used for **2**, which was recrystallized from pentane at −20 °C (40 % yield). M.p. 78 °C (decomp); ¹H NMR (400.1 MHz, C₇D₈, TMS): δ = 0.37 (s, 9H, Me₃Si), 1.02 (d, ³J(H,H) = 7.0 Hz, 12H, CH(CH₃)₂), 1.06 (d, ³J(H,H) = 7.0 Hz, 12H, CH(CH₃)₂), 3.27 (sept, ³J(H,H) = 7.0 Hz, 4H, CH(CH₃)₂), 3.72 (s, 4H, CH₂), 7.08–7.17 (m, 3H, ArH); ¹³C NMR (100.6 MHz, C₇D₈, TMS): δ = 0.04 (CH₃Si), 20.63 (CH(CH₃)₂), 21.45 (CH(CH₃)₂), 30.15 (CN₂), 51.20 (CH(CH₃)₂), 54.36 (CH₂), 124.19 (*m*-C), 127.67 (*p*-C), 147.10 (*o*-C), 158.39 (*ipso*-C); ²⁹Si NMR (39.8 MHz, C₇D₈, TMS): δ = 0.06 (Me₃Si); EI-MS (70 eV): *m/z* (%): 490 (12) [*M*⁺], 447 (4) [*M*⁺ − *i*Pr], 419 (5) [*M*⁺ − *i*Pr − N₂], 377 (100) [ArGe]; IR (C₆D₆): ν̄ = 2001 cm^{−1} (CN₂).

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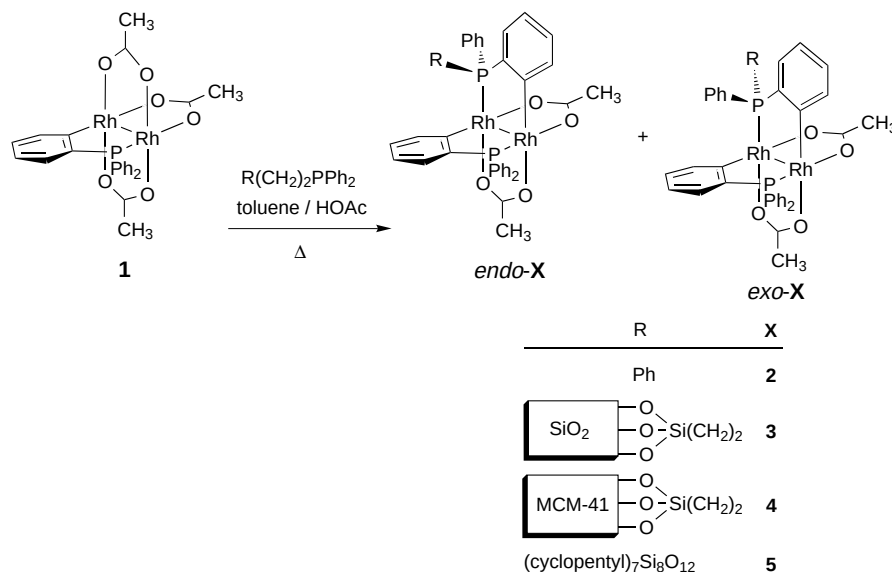
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Heterogeneous Dinuclear Rhodium(II) Hydroformylation Catalysts—Performance Evaluation and Silsesquioxane-Based Chemical Modeling**

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The extensive use of homogeneous transition metal catalysts in industrial hydroformylation processes is affected by a number of disadvantages, such as the problem of the recovery of the metal from the reaction products, expensive metal losses, and solubility limitations.^[1] Many attempts have been made to overcome these drawbacks by immobilizing metal complex catalysts on various supports, with inorganic oxide carriers being considered the most promising.^[2] Catalysts prepared by coordinative anchoring of metal complexes on a chemically modified support containing donor functions possess superior activities to those which are prepared by means of physical adsorption (supported liquid-phase catalysts, deposited catalysts, etc.), although the achievable activities are still inferior to those of the corresponding homogeneous systems because of mass-flow restrictions.^[2d, 3] Another severe problem of coordinatively anchored catalysts is their limited stability towards metal leaching. However, the exceptional stability of a rhodium catalyst that had been immobilized on a silica support by a *trans*-chelating bidentate phosphane tether has recently been reported.^[4]

Dinuclear rhodium(II) complexes $[\text{Rh}_2(\mu\text{-PC})_2(\mu\text{-O}_2\text{CR})_2]$ ($\mu\text{-PC}$ = bridging *ortho*-metalated arylphosphane ligand) catalyze the hydroformylation of styrene with high efficiency.^[5]



Scheme 1. From **1** to dinuclear rhodium(II) complexes bearing two *ortho*-metalated phosphane ligands. Axial acetic acid ligands are omitted for clarity.

The immobilization of these catalysts on amorphous silica supports as well as on MCM-41 by surface-tethered phosphane ligands appeared desirable, since a) the bridging bidentate coordination of the *ortho*-metalated phosphane ligands promises firm anchoring of the catalyst on the support (thereby reducing the problem of catalyst leaching without problems arising from *cis*-chelation^[6]) and b) the open mesoporous support structures should avoid mass-transfer problems.^[7] This objective was approached by an acid-assisted cyclometalation reaction^[8] between a surface-grafted phenylphosphane tether and the catalytic precursor **1**.^[9] Compound **1** is known to react cleanly with one equivalent of PPh_3 to give **2** (Scheme 1). The phosphane-modified silica supports were

prepared by grafting $\text{Ph}_2\text{P}(\text{CH}_2)_2\text{SiCl}_3$ ^[10] on both amorphous silica gel and on MCM-41. In case of the mesoporous support MCM-41, protection of the external surface with a layer of grafted $\text{Si}(\text{CH}_3)_2$ groups under nondiffusive conditions prior to the introduction of the phosphane tethers guaranteed the location of the tethers within the mesoporous channels.^[11] Heating **1** with an excess of phosphane-grafted silica or MCM-41 dispersed in toluene in the presence of acetic acid resulted in complete adsorption of **1** with formation of the immobilized catalysts **3** and **4**, respectively (Scheme 1).

Incompletely condensed polyhedral oligosilsesquioxanes (OSS) can be used to model the surface chemistry of silica involved in organometallic grafting reactions.^[12] Hence, for a better understanding of the processes that take place during the immobilization of the catalyst on the surface of a phosphane-modified support, we studied the analogous cyclometalation reactions between **1** and the soluble OSS model $(\text{c-C}_5\text{H}_9)_7\text{Si}_8\text{O}_{12}(\text{CH}_2)_2\text{PPh}_2$, which may itself be considered as a phosphane-modified molecular section of a silica surface.^[13]

Dinuclear rhodium(II) complexes $[\text{Rh}_2(\mu\text{-PC})_2(\mu\text{-O}_2\text{CR})_2]$ with a head-to-tail configuration of the two bridging *ortho*-metalated phosphane ligands ($\mu\text{-PC}$)—as formed exclusively under the conditions employed in this study—have backbone

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chirality.^[14] The introduction of an additional stereocenter arising from the replacement of a phenyl substituent on one of the *ortho*-metalated phosphane ligands in **2** thus results in the formation of diastereomeric products, denoted *endo* and *exo* in Scheme 1. The reaction between **1** and (C₅H₉)₇Si₈O₁₂(CH₂)₂PPh₂ afforded accordingly a mixture of two diastereomers of **5** in a ratio of 8.4:1, as revealed by ³¹P NMR spectroscopy. Subsequent crystallization yielded the pure major component of the mixture, which was characterized spectroscopically and by single-crystal X-ray diffraction^[15] to afford the first crystal structure of an OSS bearing a pendant transition metal complex.

The crystal structure of the major isomer of **5** (Figure 1) reveals that the OSS-substituent of the newly introduced phosphane ligand adopts a position *endo* with respect to the

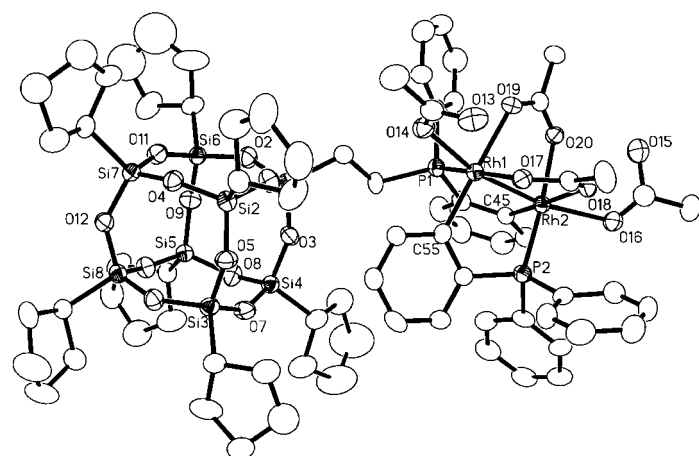


Figure 1. Molecular structure of *endo*-**5** showing the crystallographic labeling scheme. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Rh1–Rh2 2.5078(6), Rh1–P1 2.2123(13), Rh2–P2 2.2125(13), Rh1–C55 2.004(4), Rh2–C45 1.992(5), Rh1–O17 2.152(3), Rh1–O19 2.187(3), Rh2–O18 2.187(3), Rh2–O20 2.151(3), Rh1–O14 2.352(3), Rh2–O16 2.346(3); Rh1–Rh2–P2 87.80(3), Rh2–Rh1–P1 87.82(3), Rh1–Rh2–C45 97.36(13), Rh2–Rh1–C55 97.29(13), Rh2–Rh1–O19 83.95(8), Rh1–Rh2–O20 86.48(8), Rh2–Rh1–O17 86.36(8), P1–Rh1–C55 89.86(13), C55–Rh1–O17 91.53(15), O17–Rh1–O19 84.83(12), O19–Rh1–P1 93.91(9), P2–Rh2–C45 89.53(13), C45–Rh2–O20 91.52(15), O20–Rh2–O18 85.03(12), O18–Rh2–P2 94.10(9).

second *ortho*-metalated phosphane ligand of the dinuclear rhodium complex. This allows the unmetalated phenyl substituent on P1 to point towards the bridging acetate ligand on the less sterically encumbered side of the complex. This

preference clearly indicates the lower steric bulk of the 1,2-ethanediyl bridge between P1 and the silsesquioxane moiety in comparison to the unmetalated phenyl substituent, since the extremely space-demanding pending silsesquioxane unit can adopt a remote position without sterically interfering with the bulky dinuclear rhodium cluster. The observed bond lengths and angles of the dinuclear rhodium cluster moiety lie within the range of the respective values in other reported structures of [Rh₂(μ-PCl)₂(μ-O₂CR)₂] complexes.^[16]

The performance of the immobilized catalysts **3** and **4** (supported on amorphous silica and MCM-41, respectively) was evaluated in repeated hydroformylation experiments employing either styrene or 1-decene as substrates (Table 1). After each catalytic run the catalysts were recovered by filtration and reused in the subsequent experiment. Contrary to the well-known sensitivity of anchored hydroformylation catalysts towards oxygen,^[2b, 6c] exclusion of oxygen during this recovery procedure proved unnecessary; catalyst samples that were handled under air exhibited activities identical to those of samples that were kept under argon.

In the hydroformylation of styrene both **3** and **4** exhibited comparable activities and selectivities under identical conditions in the initial catalytic run. A decrease of the reaction rate by restricted mass transport within the mesoporous channels in the case of **4** was not observed. The chemoselectivity towards the formation of aldehyde products was nearly quantitative in all the experiments employing styrene as the substrate. No products arising from the hydrogenation of either the starting material or products were detected. The regioselectivity in favor of the branched aldehyde product is higher at 60 bar of CO/H₂ than at 30 bar under otherwise identical conditions. The observed level of activity as well as selectivity of the immobilized catalysts in the initial catalytic run is—within the margins of experimental errors—identical with that reported for their homogeneous counterpart **2**,^[5] thus demonstrating the advantage of coordinative anchoring. However, the initial high level of selectivity in favor of the branched product decreased steadily in each subsequent catalytic run with both **3** and **4** and at varying pressures. The bidentate bridging coordination mode of the phenylphosphane tether could not completely suppress activity losses through catalyst leaching, as the decrease of activity in consecutive experiments indicates. Some catalyst leaching clearly took place as all filtrates exhibited a low degree of hydroformylation activity after removal of the heterogeneous

Table 1. Hydroformylation of alkenes catalyzed by immobilized dinuclear rhodium(II) complexes.^[a]

Entry	Catalyst	Substrate	Run	<i>p</i> [bar]	Conv. [%]	Aldehyde [%] ^[b]	Selectivity (<i>b</i> : <i>n</i>) ^[c]	Isoalkenes [%] ^[b]	Alkane [%] ^[b]
1	3	styrene	1	60	100	> 99	14.9	–	< 1
2	3	styrene	4	60	6	> 99	7.8	–	< 1
3	4	styrene	1	60	100	> 99	15.1	–	< 1
4	4	styrene	4	60	98	> 99	6.9	–	< 1
5	4	styrene	1	30	100	> 99	11.1	–	< 1
6	4	styrene	6	30	63	> 99	3.4	–	< 1
7	2 ^[5]	styrene	–	30	100	–	11.5	–	–
8	4	1-decene	1	30	97	81	0.66	11	8
9	4	1-decene	4	30	34	62	0.47	14	24

[a] General reaction conditions: 0.0125 mmol of Rh^{II} complex, substrate/catalyst = 400/1, CO/H₂ = 1/1, solvent = toluene (10 mL). For styrene: *T* = 60 °C, *t* = 6 h; for decene: *T* = 80 °C, *t* = 4 h. [b] Referenced to converted alkene. [c] *n* = Linear aldehyde, *b* = branched aldehyde.

catalyst. The continuous decrease in selectivity in consecutive runs may therefore be ascribed to an increasing contribution of the highly active, but unselective, leached rhodium carbonyl species^[17] to the overall conversion, corresponding to a simultaneous decrease in the concentration of the immobilized species. However, the nature of the support had a dramatic effect on the degree of leaching: while catalyst **3**, immobilized on amorphous silica, had lost almost all of its initial activity after only four catalytic runs, the respective drop in activity was less pronounced for catalyst **4**, with the catalytic complex anchored inside the mesopores of MCM-41. Furthermore, an increase in pressure from 30 to 60 bar resulted in an almost negligible drop in catalytic activity for catalyst **4** during recycling.

Catalyst **4** was also employed in the hydroformylation of 1-decene. The chemoselectivity in favor of aldehyde products exhibited by **4** is in all subsequent runs significantly lower for this olefin than for styrene hydroformylation. The fraction of the hydrogenated side-product, *n*-decane, increases steadily at the expense of hydrocarbonylated products in subsequent catalytic runs, while the amount of isomerized decene by-products is not changed significantly. Simultaneously, a steady increase in regioselectivity within the aldehyde fraction towards the linear product *n*-undecanal with each consecutive run is observed, as expressed by the rise of the linear: branched aldehyde ratio (*n*:*b*) from 1.52:1 (run 1) to 2.13:1 (run 4). The low level of regioselectivity for the linear aldehyde product in the hydroformylation of 1-decene is indicative of a reactive site with a low degree of steric encumbrance.^[1]

Experimental Section

All reactions were carried out under an argon atmosphere in dry solvents using standard Schlenk techniques unless stated otherwise.

[SiO₂]₂-(CH₂)₂PPh₂: A mixture of fumed silica (5.0 g, vacuum-dried at 200 °C, 250 m² g⁻¹, 9.75 mmol SiOH^[18]), Ph₂P(CH₂)₂SiCl₃ (113 mg, 0.325 mmol), and pyridine (77 mg, 0.975 mmol) in toluene (30 mL) was stirred at 25 °C for 12 h. The solid was filtered, washed with methanol (250 mL) and diethyl ether (50 mL), and dried in vacuo at 80 °C; yield 5.052 g; ³¹P CP-MAS NMR (162 MHz): δ = -9.95; IR: ν̄ = 1443 cm⁻¹ (P-Ph).

[MCM-41]₂-(CH₂)₂PPh₂: Siliceous MCM-41 (2.5 g, vacuum-dried at 200 °C, 1000 m² g⁻¹, 19.5 mmol SiOH^[18]) was suspended in hexane (50 mL), Me₂SiCl₂ (0.034 mL, 0.28 mmol) was added at 0 °C and the mixture was allowed to warm to ambient temperature and stirred for 1 h. The volatiles were then removed in vacuo. The solid was suspended in toluene (50 mL). Ph₂P(CH₂)₂SiCl₃ (695 mg, 2 mmol) was slowly added at 0 °C, and the mixture was stirred at ambient temperature for 24 h. The released HCl was then removed by heating the mixture under reflux in a stream of dry argon for 2 h. The product was collected by filtration, washed with CH₂Cl₂ (10 × 30 mL) and dried in vacuo at 80 °C; yield 3.137 g; X-ray diffraction: 2θ₁₀₀ = 2.275°, *a* = 44.8 Å; ³¹P CP-MAS NMR (162 MHz): δ = -9.89; IR: ν̄ = 1440 cm⁻¹ (P-Ph).

3: A mixture of **1** (35 mg, 0.046 mmol) and [SiO₂]₂-(CH₂)₂PPh₂ (1.5 g, ca. 0.1 mmol PPh₂^[19]) in toluene (30 mL) was heated under reflux for 15 min. Glacial acetic acid (10 mL) was added and heating was continued for additional 1.5 h. The pink solid was collected by filtration and washed with methanol (50 mL) and diethyl ether (20 mL), and dried in vacuo; yield 1.528 g. The filtrate did not contain any residual dinuclear rhodium complex, indicating complete adsorption. ³¹P CP-MAS NMR (162 MHz): δ = 18.87 (br s, *J*(Rh,P) unresolved).

4 was prepared analogously to **3** from **1** (100 mg, 0.131 mmol) and [MCM-41]₂-(CH₂)₂PPh₂ (1.0 g, ca. 0.6 mmol PPh₂^[19]); yield 1.034 g; X-ray diffraction: 2θ₁₀₀ = 2.265°, *a* = 45.0 Å; ³¹P CP-MAS NMR (162 MHz): δ = 18.75 (br s, *J*(Rh,P) unresolved).

endo-5: A mixture of **1** (30 mg, 0.039 mmol) and (c-C₅H₉)₂Si₈O₁₂-(CH₂)₂PPh₂ (44 mg, 0.039 mmol) in toluene (20 mL) and glacial acetic acid (2 mL) was heated at 60 °C for 12 h. The solvent was removed in vacuo, and the residue was purified by chromatography on silica gel with toluene/CH₃COOH (10/1) as eluent. Collection of the first pink band and subsequent solvent removal in vacuo afforded a mixture of diastereomers of **5**. The major *endo*-component was separated by repeated chromatography on silica gel with hexane/CH₂Cl₂/CH₃COOH (70/30/2). Suitable crystals of **endo-5** for X-ray analysis were grown from CH₂Cl₂/hexane; yield 33 mg (48 %); ¹H NMR (400 MHz, CDCl₃): δ = -0.54 (m, 1 H, CH₂Si), 0.42 (m, 1 H, CH₂Si), 0.85–1.02 (m, 7 H, CH, c-C₅H₉), 1.37–1.79 (m, 56 H, CH₂, c-C₅H₉), 2.06 (m, 1 H, CH₂P), 2.14 (s, 6 H, CH₃, bridging acetate), 2.20 (m, 1 H, CH₂P), 6.43 (t, ³*J*(H,H) = 8.52 Hz, 1 H, aromatic CH), 6.66 (t, ³*J*(H,H) = 7.49 Hz, 1 H, aromatic CH), 6.70 (t, ³*J*(H,H) = 7.73 Hz, 1 H, aromatic CH), 6.76–6.87 (m, 4 H, aromatic CH), 6.96 (td, ³*J*(H,H) = 7.43, 1.76 Hz, 2 H, aromatic CH), 7.08–7.18 (m, 3 H, aromatic CH), 7.25–7.35 (m, 8 H, aromatic CH), 7.51–7.59 (m, 2 H, aromatic CH), 8.16–8.22 (m, 1 H, aromatic CH); ³¹P{¹H} NMR (101 MHz, CDCl₃): δ = 16.14 (dd, ¹*J*(Rh,P) = 166.98, ²*J*(Rh,P) = 7.35 Hz, P2), 19.93 (dd, ¹*J*(Rh,P) = 173.14, ²*J*(Rh,P) = 7.95 Hz, P1); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ = 6.40 (CH₂Si), 21.60 (d, CH₂P, ¹*J*(C,P) = 28.9 Hz), 22.26–22.70 (CH, c-C₅H₉), 23.46 (CH₃, bridging acetate), 27.03, 27.31, 27.41 (all CH₂, c-C₅H₉), 121.30 (d, *J*(C,P) = 8.8 Hz, aromatic CH), 121.85 (d, *J*(C,P) = 9.1 Hz, aromatic CH), 127.01 (d, 2 C, *J*(C,P) = 9.7 Hz, aromatic CH), 127.55 (d, 2 C, *J*(C,P) = 9.3 Hz, aromatic CH), 127.73 (d, 2 C, *J*(C,P) = 8.8 Hz, aromatic CH), 128.33, 130.27, 133.06 (all s, aromatic CH), 128.39 (d, 2 C, *J*(C,P) = 12.9 Hz, aromatic CH), 128.91 (d, 2 C, *J*(C,P) = 7.2 Hz, aromatic CH), 131.03 (d, 2 C, *J*(C,P) = 8.4 Hz, aromatic CH), 133.11 (d, 2 C, *J*(C,P) = 9.0 Hz, aromatic CH), 133.58 (d, 2 C, *J*(C,P) = 9.1 Hz, aromatic CH), 136.51 (d, *J*(C,P) = 15.8 Hz, aromatic CH), 137.91 (d, *J*(C,P) = 12.9 Hz, aromatic CH), 132.70, 133.81, 134.26, 138.21, 138.63 (all s, aromatic C), 143.95, 147.44 (all m, RhC), 179.33 (s, COO, terminal), 181.10, 181.24 (all s, COO, bridging).

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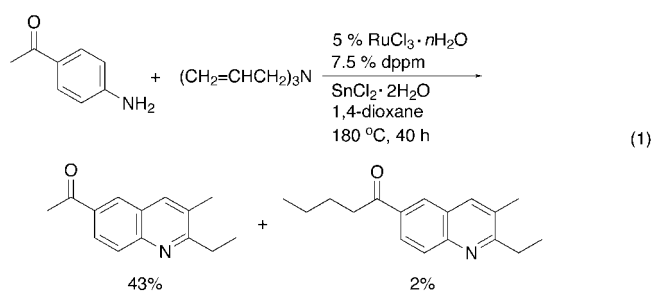
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Ruthenium-Catalyzed Regioselective α -Alkylation of Ketones: The First Alkyl-Group Transfer from Trialkylamines to the α -C Atom of Ketones**

Chan Sik Cho,* Bok Tae Kim, Myung Jin Lee, Tae-Jeong Kim, and Sang Chul Shim*

Homogeneous ruthenium-catalyzed organic reactions have been introduced for a wide variety of organic transformations and syntheses.^[1] In the course of our continuing studies on transition metal-catalyzed synthesis of N-heterocyclic compounds, we recently developed and reported a ruthenium-catalyzed synthetic approach for the formation of indoles^[2] and quinolines^[3] by alkyl-group transfer from trialkylamines to anilines (amine-exchange reaction^[4]). While studying the ruthenium-catalyzed heteroannulation between 4-aminoacetophenone and triallylamine, we found unexpectedly that careful analysis of the crude reaction mixture revealed a small amount of 1-(2-ethyl-3-methylquinolin-6-yl)pentan-1-one (2%) in addition to the expected product 1-(2-ethyl-3-methylquinolin-6-yl)ethanone [Eq. (1); dppm = bis(diphenylphosphanyl)methane].^[3a] Presumably, the former quino-



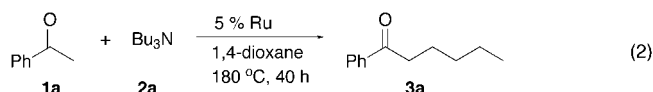
line was formed by alkylation of the latter.^[5] These observations led us to seek a general method for the ruthenium-catalyzed α -alkylation of ketones with trialkylamines. In sharp contrast to the aforementioned amine-exchange reaction, alkyl-group transfer from trialkylamines to the α -carbon atom of ketones is unprecedented. Here we report on a general method for alkyl-group transfer from trialkylamines to the α -carbon atom of ketones in the presence of a ruthenium catalyst.

First, we examined the alkylation of acetophenone (**1a**) with tributylamine (**2a**) with various ruthenium catalyst precursors [Eq. (2)]. Typically, **1a** was treated with an

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equimolar amount of **2a** in dioxane in the presence of a ruthenium catalyst precursor (5 mol %) at 180 °C for 40 h to afford 1-phenylhexan-1-one (**3a**). Table 1 shows that $\text{RuCl}_3 \cdot n\text{H}_2\text{O}/\text{PPh}_3$ and $[\text{RuCl}_2(\text{PPh}_3)_3]$ are the systems of choice for

Table 1. Ruthenium-catalyzed α -butylation of **1a** with **2a** [Eq. (2)].^[a]

Entry	Catalyst precursor	Conversion [%] of 1a ^[b]	Yield [%] of 3a ^[b]
1	$\text{RuCl}_3 \cdot n\text{H}_2\text{O}/3\text{PPh}_3$	77	70
2	$\text{RuCl}_3 \cdot n\text{H}_2\text{O}/1.5\text{dppm}^{\text{[c]}}$	32	19
3	$[\text{RuCl}_2(\text{PPh}_3)_3]$	90	69
4	$[\text{RuH}_2(\text{PPh}_3)_4]$	23	10
5	$[\text{Ru}_3(\text{CO})_{12}]$	25	4
6	$[\text{Cp}^*\text{RuCl}_2(\text{CO})]^{\text{[d]}}$	4	3
7	$[\text{Cp}^*\text{RuCl}(\text{CO})(\text{PEt}_3)]^{\text{[d]}}$	1	0

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), ruthenium catalyst (5 mol %), 1,4-dioxane (10 mL), 180 °C, 40 h, under Ar. [b] Determined by GLC. [c] dppm = bis(diphenylphosphanyl)methane. [d] $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$.

effective alkylation (entries 1 and 3). The difference between conversion and product yield could be due to reductive amination of the ketone to give a secondary amine as side product.

Table 2. Ruthenium-catalyzed α -alkylation of ketones **1** with trialkylamines **2**.^[a]

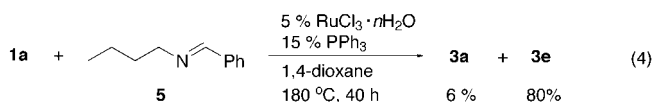
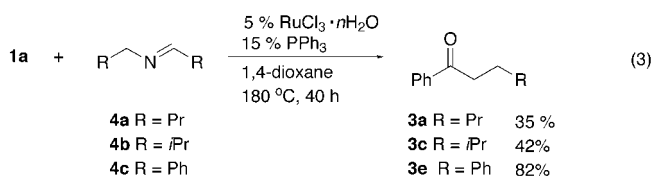
Ketone	R_3N	Product	Yield [%] ^[b]
 1a	2a R = Bu	3a R = Bu	61
	2b R = hexyl	3b R = hexyl	73
	2c R = <i>i</i> Bu	3c R = <i>i</i> Bu	77
	2d R = isopentyl	3d R = isopentyl	67
	2e R = benzyl	3e R = benzyl	30
 1b	2a	3f	32 ^[c]
 1c	2a	3g R = Bu	83
	2b	3h R = hexyl	89
	2c	3i R = <i>i</i> Bu	83
	2d	3j R = isopentyl	88
 1d	2a	3k R = Bu	70
	2b	3l R = hexyl	78
	2c	3m R = <i>i</i> Bu	75
	2d	3n R = isopentyl	78
 1e	2a	3o	81 ^[d]
 1f	2a	3p	48 ^[e,f]

[a] Reaction conditions: **1** (2 mmol), **2** (2 mmol), $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (5 mol %), PPh_3 (15 mol %), 1,4-dioxane (10 mL), 180 °C, 40 h, under Ar. [b] Yield of isolated product. [c] Carried out in a molar ratio of **2a**:**1b** = 5:1. [d] Yield determined by GLC. [e] Mixture of diastereoisomers (1:5). [f] 2,6-Dibutyl-4-phenylcyclohexanone (isomer ratio 81:13:6) was also isolated in 13 % yield.

Given these results, several ketones and amines were screened with these catalysts (Table 2). Alkyl aryl ketones **1a** and **1b** were readily alkylated with a variety of trialkylamines **2a–2e** to afford α -alkylated ketones **3a–3f** in moderate to good yields. No α,α -dialkylation was observed.^[6] A fivefold excess of amine relative to the substrate was required for the reaction of **1b**, in which case the reaction became slower and the yield was lower.^[7] Higher reaction rate and yield were observed with the benzo-fused cyclic ketone 1-indanone (**1c**).

To test for regioselectivity, dialkyl ketones **1d** and **1e** were employed, and alkylation took place exclusively at the less hindered methyl group.^[8] The reaction of 4-phenylcyclohexanone (**1f**) with **2a** gave not only 2-butyl-4-phenylcyclohexanone (**3p**) but also a small amount of 2,6-dibutyl-4-phenylcyclohexanone (13 % yield). The reaction of α,β -unsaturated ketones such as *trans*-4-phenyl-3-buten-2-one with **2a** gave no alkylated product, and the starting material was recovered.

Replacing amines with imines as alkylating agent was successful and gave the expected products [Eqs. (3) and (4)].



Here both yields and the type of the product depend upon the imine employed. For instance, imines **4** gave a single alkylation product, while imine **5** yielded two products (**3a** and **3e**) that resulted from the transfer of the alkyl or the alkylidene substituent on nitrogen. The formation of **3e** may be explained by the generation of (benzyl)(butyl)amine by reduction of the $\text{PhC}=\text{N}$ bond under the reaction conditions employed. In fact, in a separate experiment the alkylation of **1a** with *N*-butylbenzylamine afforded **3a** and **3e** in 11 % and 38 % yields, respectively.

In summary, we have developed a novel ruthenium-catalyzed highly regioselective α -alkylation of ketones with an array of trialkylamines and imines. The present ruthenium-catalyzed alkylation is a first example of alkyl-group transfer from trialkylamines and imines to the α -carbon atom of ketones. The reaction mechanism^[9, 10] and synthetic applications are currently under investigation.

Experimental Section

Typical procedure: **1a** (0.24 g, 2.0 mmol), **2a** (0.37 g, 2.0 mmol), $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (0.026 g, 0.10 mmol), PPh_3 (0.079 g, 0.30 mmol), and dioxane (10 mL) were placed in a 50-mL autoclave and allowed to react under argon at 180 °C for 40 h. The reaction mixture was filtered through a short silica gel column (CHCl_3), washed with 50 mL of 5 % HCl and dried over Na_2SO_4 . Removal of the solvent left an oil, which was purified by column chromatography (ethyl acetate:hexane 1:15) to give 1-phenylhexan-1-one (**3a**) in 61 % yield.

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- [7] Treatment of equimolar amounts of **1b** and **2a** under the usual conditions gave 2-methyl-1-phenylhexan-1-one (**3f**) in only 5% yield, and the yield of **3f** was not improved at much longer reaction times.
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Half-Metallocene Tantalum Complexes Bearing Methyl Methacrylate (MMA) and 1,4-Diaza-1,3-diene Ligands as MMA Polymerization Catalysts**

Yutaka Matsuo, Kazushi Mashima,* and Kazuhide Tani

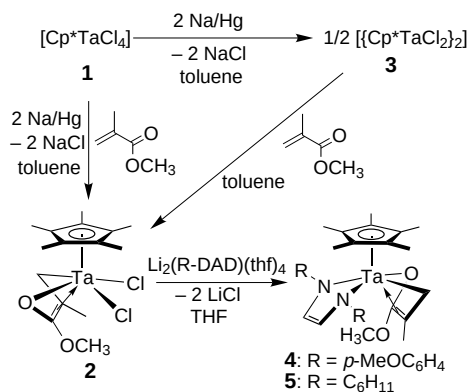
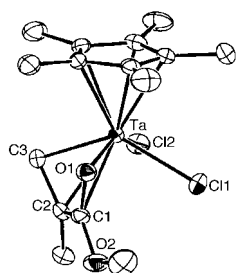
Well-defined organometallic complexes were recently reported to be single-site catalysts for the polymerization of various monomers.^[1] While enolate complexes of zirconium,^[2–5] yttrium,^[6] and samarium,^[7,8] as well as aluminum enolate complexes with Schiff base^[9] or porphyrin^[10] ligands, have been reported to be active initiators for the polymerization of polar olefinic monomers such as methyl acrylate (MA) and methyl methacrylate (MMA), enolate complexes of other transition metals have not been utilized. We sought a new metal enolate complex that can initiate polymerization of these polar monomers. Since Group 5 metals tolerate polar functional groups and are less oxophilic than the metals of Groups 3 and 4, we chose half-metallocene complexes of tantalum, cationic alkyl and alkylidene derivatives of which have already been applied in the living polymerization of ethylene^[11] and stereoselective ring-opening metathesis polymerization of norbornene^[12]. Here we report a novel tantalum initiator system and a new approach to generating catalytically active enolate species from monomer-coordinated complexes. We prepared and characterized new half-metallocene complexes of tantalum with MMA and 1,4-diaza-1,3-butadiene (DAD)^[13,14] ligands, and the tantalum–MMA complexes, upon addition of one equivalent of AlMe_3 , were found to be catalysts for the polymerization of MMA.

Scheme 1 shows the preparation of tantalum–MMA complexes from $[\text{Cp}^*\text{TaCl}_4]$ (**1**; $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$). Reduction of **1** with sodium amalgam in toluene followed by addition of MMA afforded the MMA complex $[\text{Cp}^*\text{TaCl}_2(\eta^4\text{-supine-MMA})]$ (**2**), which was alternatively prepared by treatment of the dinuclear Ta^{III} complex $[(\text{Cp}^*\text{TaCl}_2)_2]$ (**3**)^[15] with MMA. The structure of **2**^[16] (Figure 1) is essentially the same as that of $[\text{Cp}^*\text{TaCl}_2(\eta^4\text{-supine-MA})]$.^[17] Reaction of **2** with one equivalent of the dilithium salt of 1,4-bis(*p*-methoxyphenyl)-1,4-diaza-1,3-butadiene (*p*-MeOC₆H₄-DAD) or the dilithium salt of 1,4-dicyclohexyl-1,4-diaza-1,3-butadiene (Cy-DAD) in THF afforded the half-sandwich DAD complexes of tantalum **4** and **5**, respectively. The ^1H NMR spectra of **4** and **5** displayed two doublets at $\delta = 6.67$ and 6.84 ($J = 3.4$ Hz) for **4**

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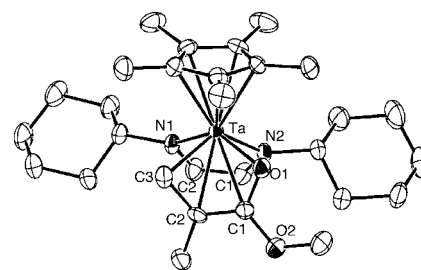
[**] We thank Professor emeritus A. Nakamura (Osaka University) for fruitful discussions. The present research was supported in part by a grant-in-aid for Scientific Research on Priority Areas “Molecular Physical Chemistry” from the Ministry of Education, Science, Culture, and Sports. Y.M. is a research fellow of the Japan Society for the Promotion of Science, 1998–2000.

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 Scheme 1. Synthesis of **4** and **5**.

 Figure 1. Molecular structure of **2**. Selected bond lengths [Å] and angles [°]: Ta–O1 2.043(3), Ta–C1 2.419(5), Ta–C2 2.403(5), Ta–C3 2.174(5); O1–Ta–C3 76.3(2), C11–Ta–Cl2 85.39(5), MMA fold angle: 104.2(3).

and $\delta = 6.44$ and 6.71 ($J = 2.4$ Hz) for **5** due to magnetically inequivalent N=CH protons of the DAD ligand. These chemical shifts together with the characteristic intense red color due to a ligand-to-metal charge-transfer band ($\lambda_{\max} = 512$ nm for **4**; 534 nm for **5**) suggest that the DAD ligand adopts an η^2 - N,N' -enediamido structure.^[18, 19] Figure 2^[20] clearly shows that the half-metallocene tantalum fragment is coordinated by an η^2 - N,N' -enediamido Cy-DAD ligand and an η^4 -supine-MMA ligand. The nitrogen atoms of the Cy-DAD ligand [sums of angles: 359.7° (N1) and 359.9° (N2)] have a trigonal-planar coordination sphere so that the filled p_π orbitals of the nitrogen atoms interact laterally with the empty d_π orbital of the tantalum center.

Table 1 summarizes the results of the polymerization of MMA with tantalum MMA complexes as catalyst precursors and alkylaluminum compounds as cocatalysts. The MMA


 Figure 2. Molecular structure of **5**. Selected bond lengths [Å] and angles [°]: Ta–O1 2.116(4), Ta–C1 2.527(7), Ta–C2 2.460(7), Ta–C3 2.207(7), Ta–N1 2.098(6), Ta–N2 2.101(6), O1–C1 1.310(10), C1–C2 1.372(8), C2–C3 1.49(1); O1–Ta–C3 78.2(2), N1–Ta–N2 75.0(2), MMA fold angle: 111.8(3), DAD fold angle: 159.7(2).

complexes **4** and **5** without the cocatalyst did not have any catalytic activity, and complex **2** in the presence of one equivalent of AlMe_3 also exhibited no catalytic activity (entry 1). The catalyst system of highest activity was the combination of **5** and one equivalent of AlMe_3 at -20°C ; the polymerization was completed within 10 min to give a PMMA with very narrow polydispersity ($M_w/M_n = 1.10$; entries 10 and 11).^[21] Polymerization with **5**/ AlMe_3 at -30°C was much slower and proceeded in a living fashion (entries 12 and 13); the M_n of the polymers increased linearly with increasing percentage monomer consumption (Figure 3). The obtained

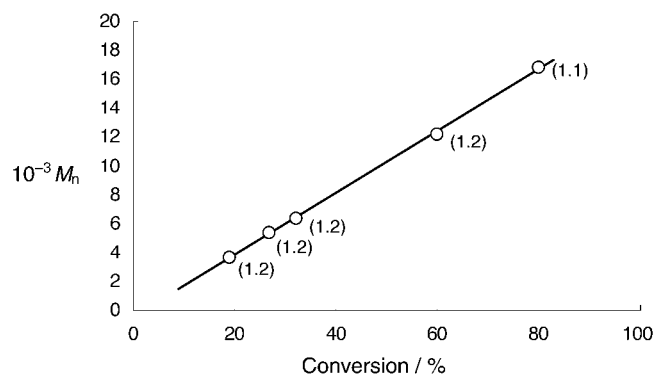
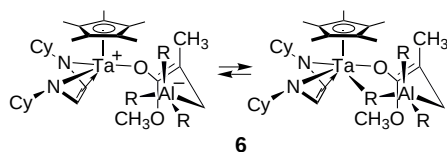

 Figure 3. Molecular weight of PMMA, prepared with **5** and one equivalent of AlMe_3 as catalyst system at -30°C versus percentage conversion. The M_w/M_n value for each data point is given in parenthesis.

 Table 1. Polymerization of methyl methacrylate with catalysis by tantalum–MMA complexes.^[a]

Entry	Precatalyst	Activator	T [°C]	t [min]	Yield ^[b] [%]	$M_n \times 10^{-3}$ ^[c]	M_w/M_n ^[c]	Tacticity ^[d] (mm/mr/rr)
1	2	AlMe_3	0	300	0	–	–	–
2	4	AlMe_3	25	300	0	–	–	–
3	4	AlMe_3	0	90	22	15.6	1.75	1/25/74
4	4	AlMe_3	0	300	74	34.8	1.83	2/25/73
5	4	AlMe_3	-20	300	4.2	90.4	1.39	2/25/73
6	5	AlMe_3	25	300	0	–	–	–
7	5	AlMe_3	0	60	99	22.0	1.3	2/24/74
8	5	AlEt_3	0	300	99	20.0	3.0	3/31/66
9	5	AlEt_2Cl	0	600	0	–	–	–
10	5	AlMe_3	-20	5	82	18.8	1.11	2/27/71
11	5	AlMe_3	-20	10	99	21.9	1.10	2/25/73
12	5	AlMe_3	-30	10	32	6.3	1.20	1/24/75
13	5	AlMe_3	-30	40	99	24.9	1.23	1/21/78
14	7	AlMe_3	0	600	0	–	–	–

[a] Polymerizations were conducted in toluene with [precatalyst] = 23.4 mM and [precatalyst]/[activator]/[monomer] = 1/1/100. [b] Yield = weight of polymer obtained/weight of monomer used. [c] Determined by GPC analysis with a polystyrene standard. [d] Determined from ^1H NMR spectra recorded in CDCl_3 at 35°C .

M_n values are approximately twice those calculated on the basis of $[MMA]_0/[initiator]_0$; it is possible that this is due to decomposition of the unstable active species **6** before



6

polymerization is initiated. Increasing the polymerization temperature affected the catalytic activity; at 0 °C the activity of **5** decreased (entry 7) and at 25 °C no polymerization occurred (entry 6). The catalyst system based on **4** was less active than that containing **5** (entries 3–5), and it also exhibited no activity at 25 °C (entry 2); this may be attributable to the electronic effect of the DAD ligand. Such temperature effects can be attributed to the thermal stability of the catalytically active enolate species that is formed on addition of $AlMe_3$ to these MMA complexes. In the case of **5**, the effect of the cocatalyst was examined; both $AlMe_3$ and $AlEt_3$ satisfactorily activated the catalyst precursor (entries 7 and 8), while $AlEt_2Cl$ resulted in no activation (entry 9).

Controlled experiments gave an insight into the active enolate species. Addition of one equivalent of $AlMe_3$ to **5** in $[D_8]$ toluene at room temperature afforded the dimethyl complex $[Cp^*TaMe_2(\eta^4-Cy-DAD)]$ (**7**), which was completely inactive in the polymerization of MMA (entry 14) but catalyzed the polymerization of ethylene in the presence of an excess of MAO. On the other hand, addition of one equivalent of $AlMe_3$ to **5** at –20 °C gave the heterodimetallic enolate species **6** together with the dimethyl complex **7** (less than 15%). Compound **6** was tentatively characterized by means of the ^1H NMR spectrum in $[D_8]$ toluene, which displayed two broad signals at $\delta=5.33$ and 6.26 due to the inequivalent $N=CH$ groups of the Cy-DAD ligand and two $AlMe$ signals at $\delta=0.05$ and 0.45 in a ratio of 1:2. These observations suggest that one of the $AlMe$ groups interacts with the electron-deficient metal center. This enolate species was thermally unstable, and was converted to the dimethyl complex **7** after 1 h at 0 °C. This is in good accordance with the temperature effects observed for the polymerization. Similar insertions of alkylaluminum compounds into zirconocene diene complexes to give heterodimetallic compounds were reported by Erker et al.^[22]

In summary, we have demonstrated a new method to generate enolate species from monomer-coordinated tantalum complexes. Tantalum–MMA complexes on treatment with one equivalent of $AlMe_3$ effectively catalyzed the polymerization of MMA. The investigation of the mechanism and the preparation and application of catalyst precursors with other monomers as ligands are under way.

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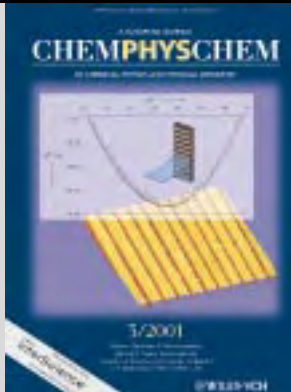
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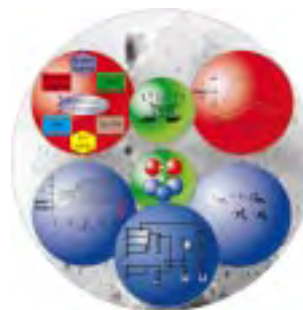
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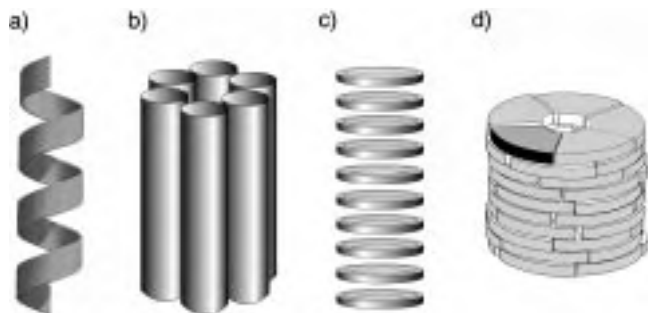
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COVER PICTURE

The cover picture shows an arrangement of ruthenium atoms representing the active site of ruthenium catalysts for ammonia synthesis. This B₅-type active site consists of three ruthenium atoms in one layer (blue spheres) and two ruthenium atoms in the layer directly above this (red spheres). This arrangement is energetically preferred, because none of the ruthenium atoms is in contact with both of the nitrogen atoms (green spheres) of the adsorbed N₂ molecule. Based on knowledge of this active site a number of catalysts were prepared by using [Ru₃(CO)₁₂] (upper green sphere) as a precursor. These catalysts were characterized (left red sphere and TEM micrograph in the background), tested using a parallel screening procedure (left and lower blue spheres), and kinetically analyzed (right blue sphere). The resulting barium-promoted Ru/MgO catalyst is the most active catalyst for ammonia synthesis to be described (right red sphere). It can be concluded that the B₅-type site also dominates the activity of the promoted catalysts (lower green sphere). The enormous catalytic potential of Ba-Ru/MgO is described by Muhler et al. on pp. 1061 ff.



Multiple strategies have been documented in recent years for the construction of tubular materials from self-organizing subunits. Cylindrical molecular compartments can be assembled by helical folding of linear species (a; see diagram), aggregation of rodlike molecules (b), stacking of molecular discs (c), or clustering of compounds with a truncated wedge-shape (d). Just as numerous are the applications of tubular materials; they are used as biosensors, novel antibiotics, biomaterials, molecular devices, and chemical catalysts.



Angew. Chem. **2001**, *113*, 1016–1041

D. T. Bong, T. D. Clark, J. R. Granja,
M. R. Ghadiri* 988–1011

Self-Assembling Organic Nanotubes

Keywords: crystal engineering •
materials science • nanotubes •
self-assembly • sensors

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>

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D. Marciu, H. C. Dorn,*
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Copper(I) Carbenes: The Synthesis of Active Intermediates in Copper-Catalyzed Cyclopropanation

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Synthesis of Conformationally Locked Carbohydrates: A Skew-Boat Conformation of L-Iduronic Acid Governs the Antithrombotic Activity of Heparin

S. K. Das, J.-M. Mallet,
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The First Phosphine Oxide Ligand Precursors for Transition Metal Catalyzed Cross-Coupling Reactions: C–C, C–N, and C–S Bond Formation on Unactivated Aryl Chlorides

G. Y. Li*

Cyclic Dimers of Metalloporphyrins as Tunable Hosts for Fullerenes: A Remarkable Effect of Rhodium(III)

J.-Y. Zheng, K. Tashiro,
Y. Hirabayashi, K. Kinbara,
K. Saigo,* T. Aida,*
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Modular Pyridinyl Peptide Ligands in Asymmetric Catalysis: Enantioselective Synthesis of Quaternary Carbon Atoms Through Cu-Catalyzed Allylic Substitutions

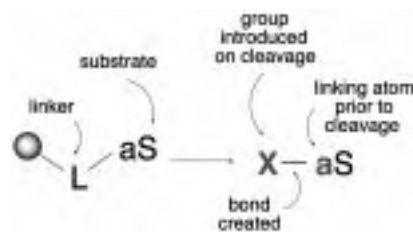
C. A. Luchaco-Cullis,
H. Mizutani, K. E. Murphy,
A. H. Hoveyda*

Direct Observation of Surface-Controlled Self-Assembly of Coordination Cages by using Atomic Force Microscopy as a Molecular Ruler

S. A. Levi, P. Guatterì,
F. C. J. M. van Veggel,
G. J. Vancso, E. Dalcanele,
D. N. Reinhoudt*

What is “tracelessness” really? The term refers to solid-phase organic synthesis in which the cleaved product contains no vestige of the linker; at least three quite distinct definitions are in current use. Nomenclature is essential for the efficient communication of ideas and a more rigid and comprehensible terminology (see scheme) will clear the mists from a rather cloudy aspect of this very important field.

Angew. Chem. **2001**, *113*, 1042–1063



A. C. Comely,*
S. E. Gibson (née Thomas) . . 1012–1032

Tracelessness Unmasked: A General Linker Nomenclature

Keywords: combinatorial chemistry • solid-phase synthesis • traceless linkers

ESSAY

Struggling with nature is certainly a familiar feeling to many of us. This particular metaphor began life, however, after another wrestling bout, in a striking classical allusion by Francis Bacon in 1605. We trace the evolution of the metaphor through the centuries and the way it has been invoked in opposition to science. Is it possible to experiment without intrusion?

Angew. Chem. **2001**, *113*, 1065–1068

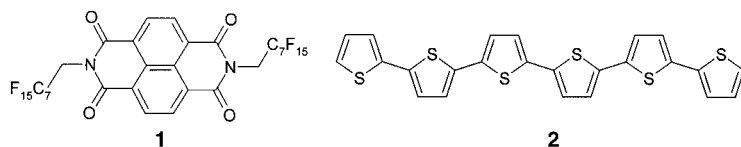
R. Hoffmann,*
P. Laszlo* 1033–1036

Protean

Keywords: history of chemistry • history of science

HIGHLIGHTS

Comparatively simple organic compounds such as naphthalenebisimides (**1**) and oligothiophenes (**2**) could become mass products in future flexible electronic devices. Several research groups have already made significant advances towards this. The next challenge to be mastered is the controlled deposition of substances from solution.



Angew. Chem. **2001**, *113*, 1069–1071

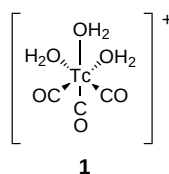
F. Würthner* 1037–1039

Plastic Transistors Reach Maturity for Mass Applications in Microelectronics

Keywords: conducting materials • microelectronics • naphthaleneimides • oligothiophenes • semiconductors

You believe that organometallic compounds are sensitive towards air and moisture and can only be handled under an inert atmosphere? Wrong! Recent work by several groups shows how organometallic compounds, such as the Tc compound **1**, are successfully used for the detection of biomolecules in an aerobic, aqueous environment. Using **1**, the radiolabeling of single-chain antibody fragments and serotonergic receptors in the central nervous system has been possible for the first time.

Angew. Chem. **2001**, *113*, 1072–1076



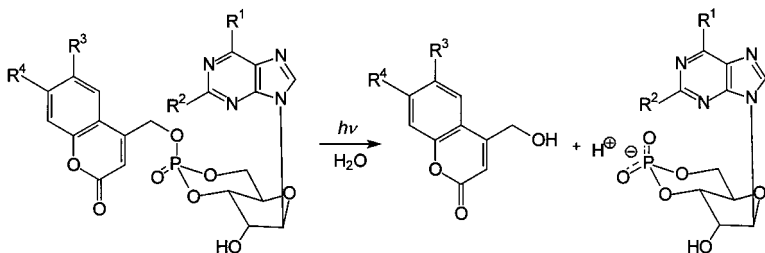
N. Metzler-Nolte* 1040–1043

Labeling of Biomolecules for Medicinal Applications—Bioorganometallic Chemistry at Its Best

Keywords: bioinorganic chemistry • bioorganometallic chemistry • biosensors • medicinal chemistry • ruthenium • technetium

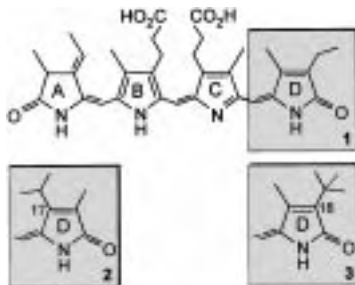


Caged cyclic nucleotides exhibiting remarkable advantageous properties have been developed through the use of novel photolabile coumarinylmethyl protecting groups (see scheme). They serve as excellent intracellular sources of cAMP and cGMP and allow the study of spatial- and time-dependent aspects of cyclic nucleotide signaling.



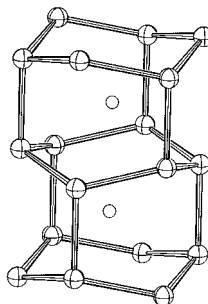
Angew. Chem. **2001**, *113*, 1078–1080

The assembly kinetics of open-chain tetrapyrroles in a recombinant apo-phytochrome and the thermal reversal of the P_{fr} to the P_r form of the phytochrome are strongly affected by steric interactions between the protein and the chromophore. Relative to the chromoprotein with a naturally occurring chromophore (**1**), bulkier alkyl groups on ring D regioselectively retard the incorporation and covalent binding (whereby C17 derivatives, particularly the 17- $\text{CH}(\text{CH}_3)_2$ derivative **2**, have a larger effect than C18 derivatives), and either decrease or increase the thermal stability of the P_{fr} form with increasing substituent size at C17/C18, respectively (the 18- $\text{C}(\text{CH}_3)_3$ derivative **3** shows the largest effect here).



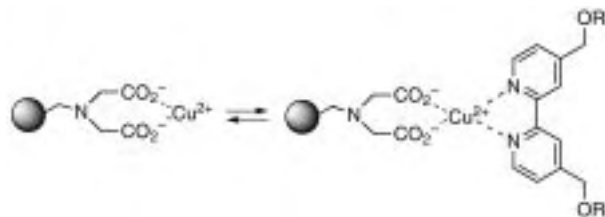
Angew. Chem. **2001**, *113*, 1080–1082

At 4 GPa and 900°C, hexagonal high-pressure LiGe—a Zintl phase—with a new structural motif was prepared: isolated hexagonal channels built up by three-coordinate Ge^- ions. These channels consist of puckered germanium six-membered rings of distorted chairs and boats (see picture). Li^+ counterions are found in the centers of the channels and in the symmetry-equivalent positions between the channels.



Angew. Chem. **2001**, *113*, 1085–1088

Simple purification of compounds can be achieved using a bipyridine unit as a tag and resin-bound metal ions. The usefulness of this method (see scheme) is demonstrated by the multistep synthesis of a small library of hydantoins and benzodiazepines.



Angew. Chem. **2001**, *113*, 1088–1090

V. Hagen,* J. Bendig, S. Frings,
T. Eckardt, S. Helm, D. Reuter,
U. B. Kaupp 1046–1048

Highly Efficient and Ultrafast
Phototriggers for cAMP and cGMP by
Using Long-Wavelength UV/Vis-
Activation

Keywords: ion channels • nucleotides •
photolysis • protecting groups • signal
transduction

U. Robben, I. Lindner, W. Gärtner,*
K. Schaffner 1048–1050

Analysis of the Topology of the
Chromophore Binding Pocket of
Phytochromes by Variation of the
Chromophore Substitution Pattern

Keywords: chromophores •
isomerization • kinetics •
photochromism • phytochromism •
tetrapyrroles

J. Evers,* G. Oehlinger 1050–1053

Isolated Hexagonal Channels Built up by
Three-Connected Ge^- Ions in LiGe at
High Pressure

Keywords: germanium • high-pressure
chemistry • lithium • structure
elucidation • Zintl phases

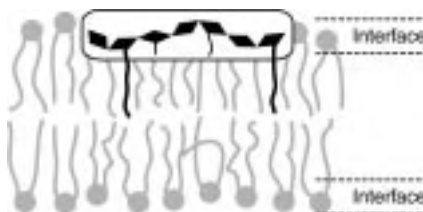
S. V. Ley,* A. Massi, F. Rodríguez,
D. C. Horwell, R. A. Lewthwaite,
M. C. Pritchard,*
A. M. Reid 1053–1055

A New Phase-Switch Method for
Application in Organic Synthesis
Programs Employing Immobilization
through Metal-Chelated Tagging

Keywords: chelates • combinatorial
chemistry • immobilization • N ligands •
separation methods

A double lipid-modified peptide

which mimics the seven amino acids of the C terminus of the N-Ras protein has been investigated by high-resolution ^1H magic angle spinning NMR spectroscopy. The axially symmetric motion of the peptide in the bilayer decreases the NMR line widths, which facilitates signal assignment and localization of the peptide in the membrane. The peptide is located in the lipid/water interface of the lipid membrane (see schematic representation).



Angew. Chem. **2001**, *113*, 1083–1085

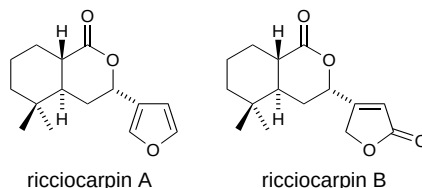
D. Huster, K. Kuhn, D. Kadereit,
H. Waldmann, K. Arnold* .. 1056–1058

^1H High-Resolution Magic Angle
Spinning NMR Spectroscopy for the
Investigation of a Ras Lipopeptide in a
Lipid Membrane

Keywords: lipids • membranes •
NMR spectroscopy • peptides

The furanosesquiterpene lactone

ricciocarpin A isolated from a liverwort displays high molluscicidal activity. By twofold application of the catalytic ring-closing metathesis a fast access to the enantiomerically pure title compounds was achieved, and their absolute configuration determined.



ricciocarpin A

ricciocarpin B

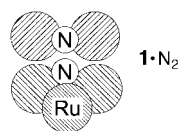
Angew. Chem. **2001**, *113*, 1091–1093

C. Held, R. Fröhlich,
P. Metz* 1058–1060

Enantioselective Synthesis of the
Ricciocarpins A and B

Keywords: metathesis • natural products •
sesquiterpenes • structure elucidation •
total synthesis

A high potential to save energy in the production of ammonia is possible with the ruthenium catalysts developed by a knowledge-based approach using a parallel screening procedure. The high activity of these catalysts is dominated by the B_5 -type site **1**.



H. Bielawa, O. Hinrichsen, A. Birkner,
M. Muhler* 1061–1063

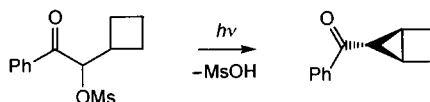
The Ammonia-Synthesis Catalyst of the
Next Generation: Barium-Promoted
Oxide-Supported Ruthenium

Keywords: ammonia synthesis •
heterogeneous catalysis • ruthenium •
screening methods

Angew. Chem. **2001**, *113*, 1093–1096

Especially highly substituted cyclopropanes

can be produced with a new photochemical approach. Starting with aromatic ketones that bear a leaving group adjacent to the carbonyl carbon atom, photolysis leads to the formation of 1,3-diradicals, which efficiently cyclize to cyclopropanes (see scheme; Ms = MeSO_2).



P. Wessig,* O. Mühling 1064–1065

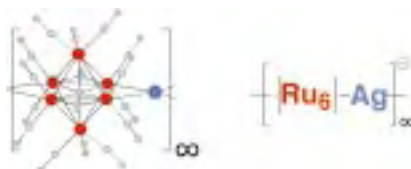
A New Photochemical Route to
Cyclopropanes

Keywords: bicycles • cyclopropanes •
diradicals • Norrish–Yang reaction •
photochemistry

Angew. Chem. **2001**, *113*, 1099–1101

Surprisingly stable

are the first cluster-containing molecular wires prepared by self-assembly of hexaruthenium cluster anions with silver cations. X-ray characterization reveals a unique structure with infinite, heteroleptic metal–metal bonded anionic chains (see picture) that are isolated by layers of counterions.



T. Nakajima, A. Ishiguro,
Y. Wakatsuki* 1066–1068

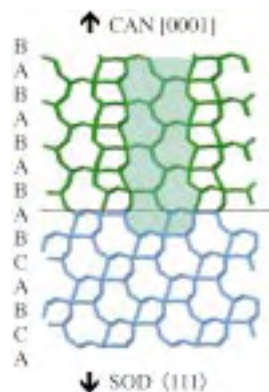
Formation of Super Wires of Clusters by
Self-Assembly of Transition Metal Cluster
Anions with Metal Cations

Keywords: cluster compounds •
coordination polymer • ruthenium • self-
assembly • silver

Angew. Chem. **2001**, *113*, 1096–1099

Parallel hexagonal prisms of cancrinite (CAN) with channels perpendicular to the substrate surface were obtained by heteroepitaxial growth on millimeter-sized sodalite (SOD) single crystals. The experiment was planned on the basis of a model in which the ABABAB stacking sequences along the cancrinite [0001] direction were connected to the ABCABC sequence along the sodalite $\langle 111 \rangle$ direction (see schematic diagram).

Angew. Chem. **2001**, *113*, 1103–1105



T. Okubo,* T. Wakiyama, J. Plévert,
S. Nair, M. Tsapatsis, Y. Ogawa,
H. Komiyama, M. Yoshimura,
M. E. Davis 1069–1071

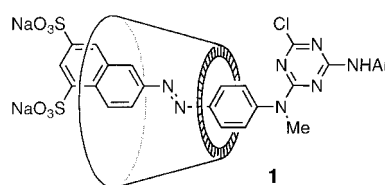
Heteroepitaxial Growth of a Zeolite

Keywords: crystal growth • microporosity
• zeolites



A “cyclodextrin coat” dramatically enhances the stability of an azo dye towards reductive bleaching, oxidative bleaching, and photo-bleaching as is demonstrated by the rotaxane **1**. This compound is obtained as a single isomer in high yield from the amine-substituted dye and trichlorotriazine in water in the presence of the cyclodextrin.

Angew. Chem. **2001**, *113*, 1105–1108



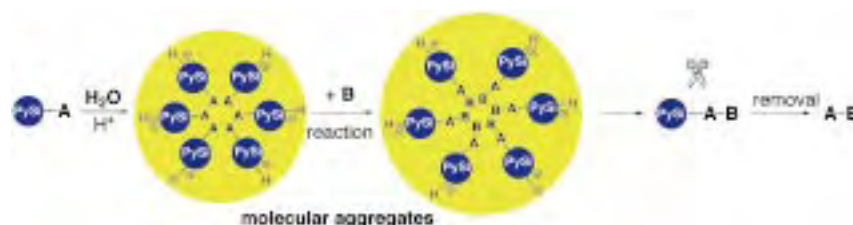
M. R. Craig, M. G. Hutchings,
T. D. W. Claridge,
H. L. Anderson* 1071–1074

Rotaxane-Encapsulation Enhances the
Stability of an Azo Dye, in Solution and
when Bonded to Cellulose

Keywords: azo compounds •
cyclodextrins • dyes/pigments •
rotaxanes • supramolecular chemistry



Dramatic rate enhancements are observed in aqueous Diels–Alder reactions between 1,3-dienes substituted with 2-pyridyldimethylsilyl (PySi) groups and *p*-benzoquinone in the presence of HCl. The hydrophilic PySi group induces molecular aggregation in water, thus enabling organic reactions to occur at hydrophobic reaction sites located within the aggregates (see scheme).



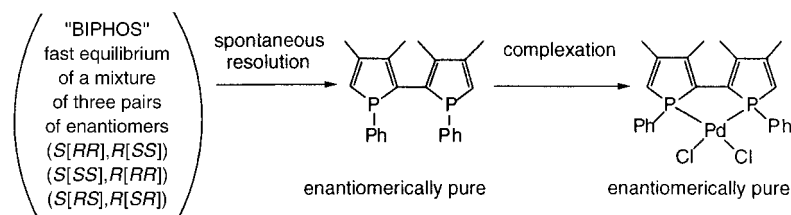
Angew. Chem. **2001**, *113*, 1108–1110

K. Itami, T. Nokami,
J.-i. Yoshida* 1074–1076

2-Pyridyldimethylsilyl as a Removable
Hydrophilic Group in Aqueous Diels–
Alder Reactions

Keywords: aggregation • cycloaddition •
silicon • solvent effects • surfactants

Enantiomerically pure BIPHOS was obtained by spontaneous resolution through the crystallization of a racemic mixture, without the use of chemical or physical chiral auxiliaries, and was used in the synthesis of the enantiomerically pure complex $[\text{PdCl}_2(\text{biphos})]$ (see scheme). The complex proved to be efficient in catalytic asymmetric allylic substitutions with 80% *ee*.



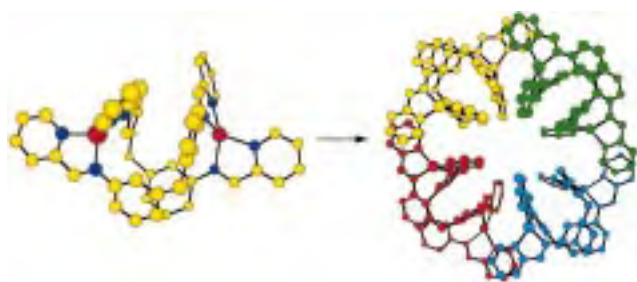
Angew. Chem. **2001**, *113*, 1110–1112

O. Tissot, M. Gouygou,*
F. Dallemer, J.-C. Daran,
G. G. A. Balavoine* 1076–1078

The Combination of Spontaneous
Resolution and Asymmetric Catalysis:
A Model for the Generation of Optical
Activity from a Fully Racemic System

Keywords: allylation • asymmetric
catalysis • P ligands • palladium •
spontaneous resolution

Arc-shaped helicate units are readily prepared from simple pyridylimine ligands. The arc-shaped topography controls their aggregation and a four-unit circular array of 2.5 nm diameter results (see scheme).



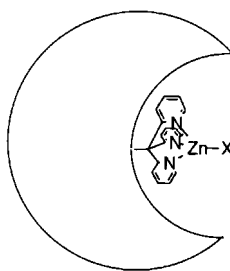
Angew. Chem. **2001**, *113*, 1113–1115

L. J. Childs, N. W. Alcock,
M. J. Hannon* 1079–1081

Assembly of Nano-Scale Circular
Supramolecular Arrays Through π – π
Aggregation of Arc-Shaped Helicate
Units

Keywords: helical structures • N ligands •
nanostructures • self-assembly •
supramolecular chemistry

Incorporation of a tripodal N_3 -donor ligand at the base of a designed molecular cleft generated inside a high molecular weight dendritic structure (see picture) allows the coordination behavior of the ligand to be controlled. This approach, using designed dendrimer clefts, has the potential to be extended to a range of different coordination environments.



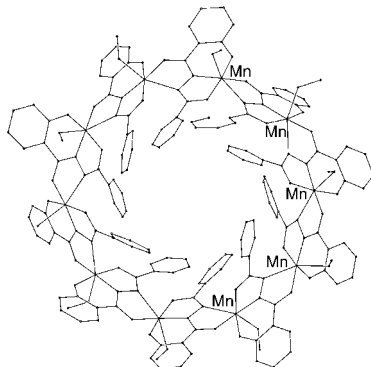
Angew. Chem. **2001**, *113*, 1115–1118

M. J. Hannon,* P. C. Mayers,
P. C. Taylor* 1081–1084

A Dendritic Structure Containing a
Designed Cleft which Controls Ligand
Coordination Behavior in an Analogous
Way to Proteins

Keywords: biomimetic chemistry •
coordination chemistry • dendrimers •
N ligands • zinc

A planar decanuclear 30-membered core ring is present in the new manganese (see picture) and iron [30]azametallacrown-10 compounds. These compounds were prepared by using the pentadentate ligand *N*-phenylsalicylhydrazide, and the metal atoms in each ring adopt a propeller configuration and have alternating Δ/Λ stereochemistries.



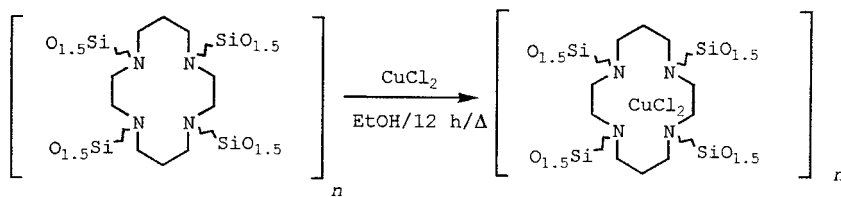
Angew. Chem. **2001**, *113*, 1118–1121

S.-X. Liu,* S. Lin, B.-Z. Lin, C.-C. Lin,
J.-Q. Huang 1084–1087

[30]Metallacrown-10 Compounds:
[Mn(C₁₄H₉N₂O₃)(CH₃OH)]₁₀ · 5 CH₂Cl₂ ·
16 CH₃OH · H₂O and
[Fe(C₁₄H₉N₂O₃)(CH₃OH)]₁₀ · 3 CH₂Cl₂ ·
12.5 CH₃OH · 5 H₂O

Keywords: crown compounds • iron •
manganese • metallacrown compounds •
supramolecular chemistry

Two routes, two materials: metal salts are incorporated into cyclam-containing hybrid materials either by the polycondensation of metal salt/silylated-cyclam complexes or by the direct incorporation of metal salts into the xerogels (see scheme). These routes are not equivalent, only the latter gives products showing metal–metal interactions. This result suggests a new coordination chemistry within nanostructured hybrid materials.



Angew. Chem. **2001**, *113*, 1121–1124

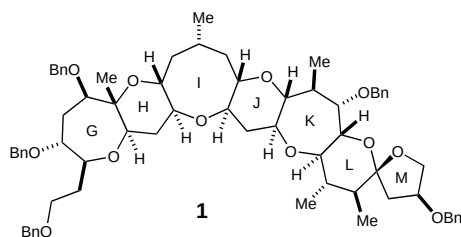
G. Dubois, C. Reyé, R. J. P. Corriu,*
S. Brandès, F. Denat,
R. Guillard* 1087–1090

Coordination Chemistry in the Solid:
Study of the Incorporation of Cu^{II} into
Cyclam-Containing Hybrid Materials

Keywords: copper • EPR spectroscopy •
macrocycles • metal–metal interactions •
sol–gel process



Access to polycyclic polyethers is facilitated by a synthetic strategy involving two-step *B*-alkyl Suzuki coupling reactions for the stereo-selective construction of the poly-ether skeleton. Thus, a convergent synthetic route to the heptacyclic GHIJKLM ring system **1** of ciguatoxin, a marine algal toxin implicated in ciguatera fish poisoning, was developed. Bn = benzyl.



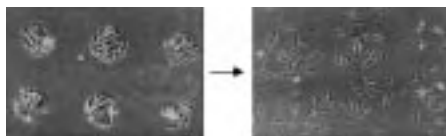
H. Takakura, K. Noguchi, M. Sasaki,*
K. Tachibana 1090–1093

Synthetic Studies on Ciguatoxin:
A Highly Convergent Synthesis of the
GHIJKLM Ring System Based on
B-Alkyl Suzuki Coupling

Keywords: ciguatoxin • cross-coupling •
natural products • polycycles • synthetic
methods

Angew. Chem. **2001**, *113*, 1124–1127

A dynamic surface can “turn on” the migration of adherent cells. This dynamic property is based on a self-assembled monolayer that presents hydroquinone groups. Electrochemical oxidation converts the hydroquinone into the corresponding benzoquinone, which then undergoes a Diels–Alder reaction with a conjugate of cyclopentadiene and a peptide ligand. This in situ modification of the substrate gives a surface that promotes cell migration (see scheme).



M. N. Yousaf, B. T. Houseman,
M. Mrksich* 1093–1096

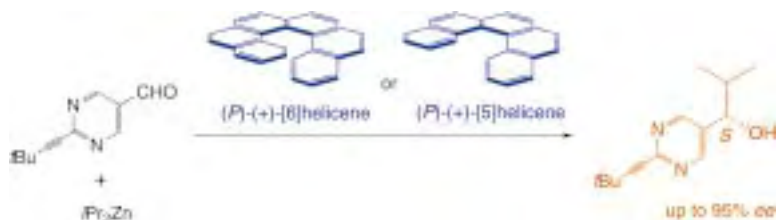
Turning On Cell Migration with
Electroactive Substrates

Keywords: bioorganic chemistry • cell
migration • Diels–Alder reaction •
monolayers • oxidation

Angew. Chem. **2001**, *113*, 1127–1130



Helicenes without any heteroatoms have been shown for the first time to act as chiral inducers in the highly enantioselective addition of diisopropylzinc to an aldehyde (see scheme).



I. Sato, R. Yamashima, K. Kadowaki,
J. Yamamoto, T. Shibata,
K. Soai* 1096–1098

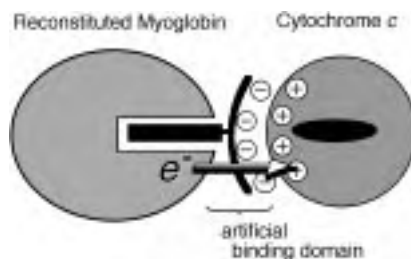
Asymmetric Induction by Helical
Hydrocarbons: [6]- and [5]Helicenes

Keywords: asymmetric amplification •
asymmetric catalysis • autocatalysis •
chirality • helical structures

Angew. Chem. **2001**, *113*, 1130–1132



Protein–protein recognition at a molecular level was investigated and its importance in interprotein electron transfer (ET) assessed by using novel synthetic models. The binding properties and overall ET reaction processes (see scheme) were controlled by the interfacial dynamics within the reconstituted myoglobin–cytochrome *c* complex.



Y. Hitomi, T. Hayashi,* K. Wada,
T. Mizutani, Y. Hisaeda,
H. Ogoshi 1098–1101

Interprotein Electron Transfer Reaction
Regulated by an Artificial Interface

Keywords: electron transfer • heme
proteins • myoglobin • protein–protein
recognition • zinc

Angew. Chem. **2001**, *113*, 1132–1135

Mesopore formation in zeolite Y upon hydrothermal treatment results in cavities inside the zeolite crystals rather than cylindrical pores that connect the external surface to the interior of the crystal. This conclusion follows from the three-dimensional visualization of the mesopores. The three images below show the development of these micropores upon extended hydrothermal treatment.



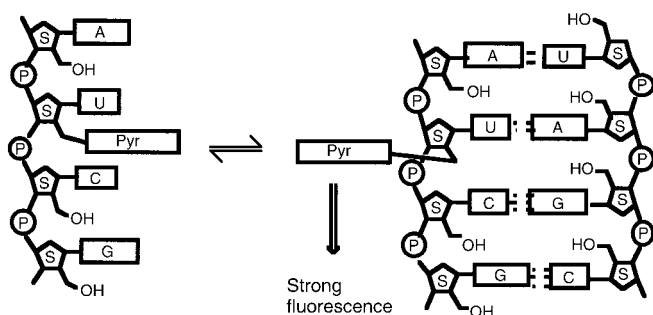
Angew. Chem. **2001**, *113*, 1136–1138

A. H. Janssen, A. J. Koster,
K. P. de Jong* 1102–1104

Three-Dimensional Transmission
Electron Microscopic Observations of
Mesopores in Dealuminated Zeolite Y

Keywords: catalysts • electron
microscopy • mesoporosity • zeolites

Labeling the 2'-hydroxy function of RNA with a pyrenylmethyl group (Pyr) provides a useful probe of RNA because of its high fluorescent quantum efficiency on binding. The fluorescence exhibits sequence specificity and binds with a high affinity (see schematic representation).



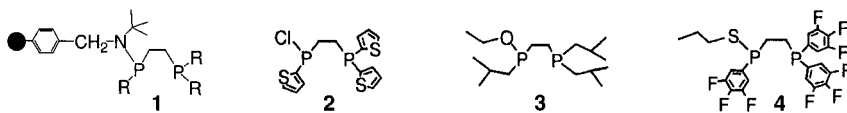
Angew. Chem. **2001**, *113*, 1138–1140

K. Yamana,* H. Zako, K. Asazuma,
R. Iwase, H. Nakano,
A. Murakami 1104–1106

Fluorescence Detection of Specific RNA
Sequences Using 2'-Pyrene Modified
Oligoribonucleotides

Keywords: fluorescence •
oligonucleotides • RNA recognition

A simple route to new diphosphane ligands: Merrifield's resin was used to construct diphosphanes of the general formula **1** that could be cleaved by reaction with PCl_3 , alcohols, or thioalcohols to provide ligands such as **2–4** in solution.



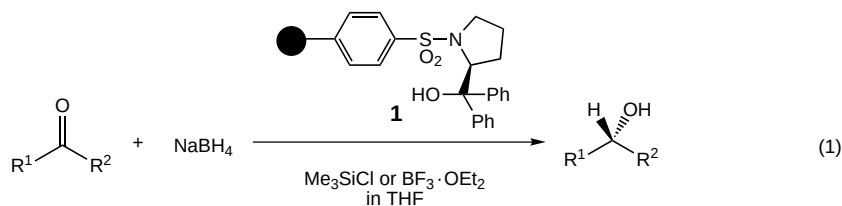
Angew. Chem. **2001**, *113*, 1140–1143

G. Y. Li,* P. J. Fagan,
P. L. Watson 1106–1109

Versatile Approaches to the Polymer-
Supported Synthesis of Bidentate
Phosphorus-Containing Ligands

Keywords: combinatorial chemistry •
homogeneous catalysis • P ligands •
phosphanes • solid-phase synthesis

Two remarkable reducing agents $\text{NaBH}_4/\text{Me}_3\text{SiCl}$ (or $\text{BF}_3 \cdot \text{OEt}_2$) in combination with a new kind of chiral, polymer-supported *N*-sulfonamide catalyst **1** were applied to the reduction of prochiral ketones giving excellent chemical yields and enantiomeric excesses [Eq. (1)].



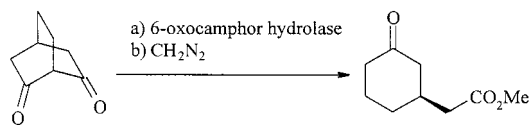
Angew. Chem. **2001**, *113*, 1143–1145

J.-b. Hu, G. Zhao,*
Z.-d. Ding 1109–1111

Enantioselective Reduction of Ketones
Catalyzed by Polymer-Supported
Sulfonamide Using $\text{NaBH}_4/\text{Me}_3\text{SiCl}$
(or $\text{BF}_3 \cdot \text{OEt}_2$) as Reducing Agent

Keywords: asymmetric synthesis •
heterogeneous catalysis • reductions •
sulfonamides

Unsymmetrical is beautiful: Enzymatic desymmetrization offers a mild route to chiral synthons with, in principle, 100% yield and absolute optical purity. The technique has been applied to bicyclic β -diketones for the first time, through a novel enzymatic retro-Claisen reaction, to yield chiral cyclic keto acids in up to 91% yield and 94% *ee* (see scheme, step a).



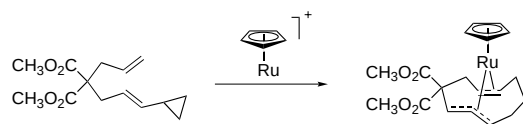
Angew. Chem. **2001**, *113*, 1145–1148

G. Grogan,* J. Graf, A. Jones, S. Parsons, N. J. Turner,* S. L. Flitsch* . 1111–1114

An Asymmetric Enzyme-Catalyzed Retro-Claisen Reaction for the Desymmetrization of Cyclic β -Diketones

Keywords: biotransformations • enzyme catalysis • hydrolases • hydrolysis

 **The reaction of coordinatively unsaturated ruthenium(II)** with a tethered (alkenylvinyl)cyclopropane results in the preparation of the first (cyclodecadienyl)ruthenium complex (see scheme; open coordination sites on the ruthenium center may be occupied by the solvent (acetone) or acetonitrile). This unprecedented reaction raises intriguing mechanistic and synthetic possibilities.



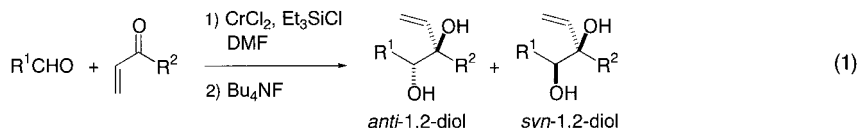
Angew. Chem. **2001**, *113*, 1148–1150

B. M. Trost,* F. D. Toste ... 1114–1116

Synthesis of the First (1-3:6,7- η -Cyclodecadienyl)ruthenium Complex by the Intramolecular Reaction of an Alkene and a Vinylcyclopropane

Keywords: allyl complexes • C–H activation • cycloisomerization • ruthenium • vinylcyclopropanes

Efficient trapping of chromium enolates in the presence of Et_3SiCl gives silyl enol ethers. This trapping changes the course of the reaction between α,β -unsaturated ketones and aldehydes from a sequential aldol–cyclopropanol formation to a cross pinacol-type coupling reaction [Eq. (1); for example, $\text{R}^1 = n\text{-C}_8\text{H}_{17}$, $\text{R}^2 = \text{Ph}(\text{CH}_2)_2$]. The *anti/syn* ratios of the 1,2-diols depend on the reaction temperature.



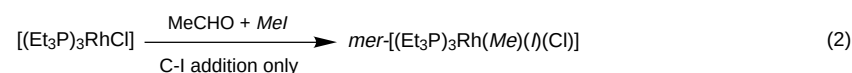
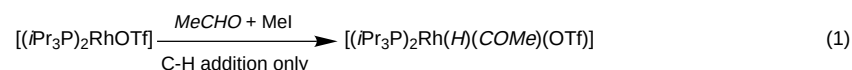
Angew. Chem. **2001**, *113*, 1150–1153

K. Takai,* R. Morita, C. Toratsu 1116–1119

Stereoselective Cross Pinacol-Type Coupling between α,β -Unsaturated Ketones and Aldehydes Mediated by Chromium(II) and R_3SiCl

Keywords: aldehydes • chromium • diols • ketones • pinacol coupling

The strikingly different reactivity of similar complexes of the type $[\text{P}_n\text{RhX}]$ is strongly dependent on the number and nature of the trialkylphosphane (P) and of the anionic ligand (X), and can be selectively directed to the oxidative addition of either aldehydes or MeI [Eqs. (1) and (2)].



Angew. Chem. **2001**, *113*, 1153–1156

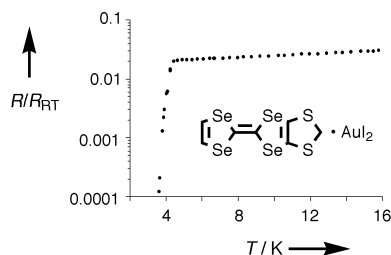
R. Goikhman, D. Milstein* 1119–1122

Ligand-Controlled Chemoselectivity in the Classical Oxidative Addition Reactions of MeI and Aldehydes to Rhodium(I) Complexes

Keywords: aldehydes • chemoselectivity • oxidative addition • rhodium



The radical cationic salt of methylenedithiotetraselenafulvalene (MDT-TSF), shown in the picture, was formed on its treatment with AuI_2^- . The salt showed a superconducting transition at 4.5 K (onset) at ambient pressure. The crystal structure of the MDT-TSF cation is completely planar and stacked along its *a*-axis; the calculated overlap integral is five times greater in the intrastack compared to the interstack direction and the material is therefore quasi one-dimensional.



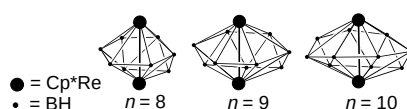
K. Takimiya,* Y. Kataoka, Y. Aso,
T. Otsubo,* H. Fukuoka,
S. Yamanaka 1122–1125

Quasi One-Dimensional Organic
Superconductor MDT-TSF · AuI_2 with
 $T_c = 4.5$ K at Ambient Pressure

Keywords: conducting materials • radical ions • selenium • superconductors

Angew. Chem. **2001**, *113*, 1156–1159

Different cluster–structure electron-counting rules to those of either boranes or metallaboranes of later transition metals are obeyed by the metallaboranes formed from the earlier transition metals. This principle is confirmed by the existence and structures of the homologous series of rhenaboranes $[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$, $n = 7–10$ (see scheme).



S. Ghosh, M. Shang, Y. Li,
T. P. Fehlner* 1125–1128

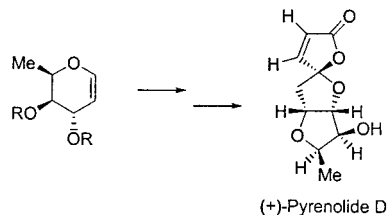
Synthesis of $[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$ $n = 8–10$:
Metal Boride Particles that Stretch the
Cluster Structure Paradigms

Keywords: boron • carboranes • cluster compounds • rhenium

Angew. Chem. **2001**, *113*, 1159–1162



The direct stereoselective I^{III} -mediated oxidative ring contraction of a protected 6-deoxy-D-gulal substrate to form a highly functionalized tetrahydrofurfural intermediate is a key step in the first total synthesis of (+)-pyrenolide D (see scheme; $\text{R} = \text{TBS} = \text{tert-butyltrimethylsilyl}$).



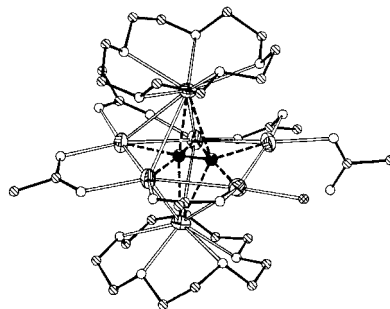
K. M. Engstrom, M. R. Mendoza,
M. Navarro-Villalobos,
D. Y. Gin* 1128–1130

Total Synthesis of (+)-Pyrenolide D

Keywords: glycals • hypervalent compounds • pyrenolide • ring contractions • total synthesis

Angew. Chem. **2001**, *113*, 1162–1164

Silver double salts containing embedded C_2^{2-} ions have been isolated by using [15]crown-5 (15C5) as a structure-directing agent. Unprecedented low dimensionalities are found for these compounds, which exist either as discrete molecules or as a zigzag chain. They feature different kinds of silver cages each sandwiched by a pair of η^5 -15C5 ligands: pentagonal bipyramidal $\text{C}_2@Ag_7$ (see picture) and $(\text{C}_2)_2@Ag_{13}$ double cage (two square antiprisms sharing a common triangular face).



Q.-M. Wang, T. C. W. Mak* . 1130–1133

Crown-Ether-Directed Assembly of
Discrete and One-Dimensional Silver
Aggregates Containing Embedded
Acetylenediide

Keywords: argentophilicity • carboxylato complexes • cluster compounds • crown compounds • silver

Angew. Chem. **2001**, *113*, 1164–1167



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BOOKS

Contents

Contemporary Instrumental Analysis	Kenneth A. Robinson, J. F. Robinson	<i>R. Zenobi</i> 1135
Comprehensive Natural Products Chemistry	Sir Derek Barton, K. Nakanishi, O. Meth-Cohn	<i>H.-G. Schmalz</i> 1135
Molecular Descriptors in QSAR/QSPR	Mati Karelson	<i>H. Kubinyi</i> 1136
Clean Synthesis using Porous Inorganic Solid Catalysts and Supported Reagents	James H. Clark, C. N. Rhodes	<i>G. Kaupp</i> 1137



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SERVICE

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• Contents of Chemistry— A European Journal	985	• Preview	1142
• Keywords	1140	• Classifieds	A33, A35

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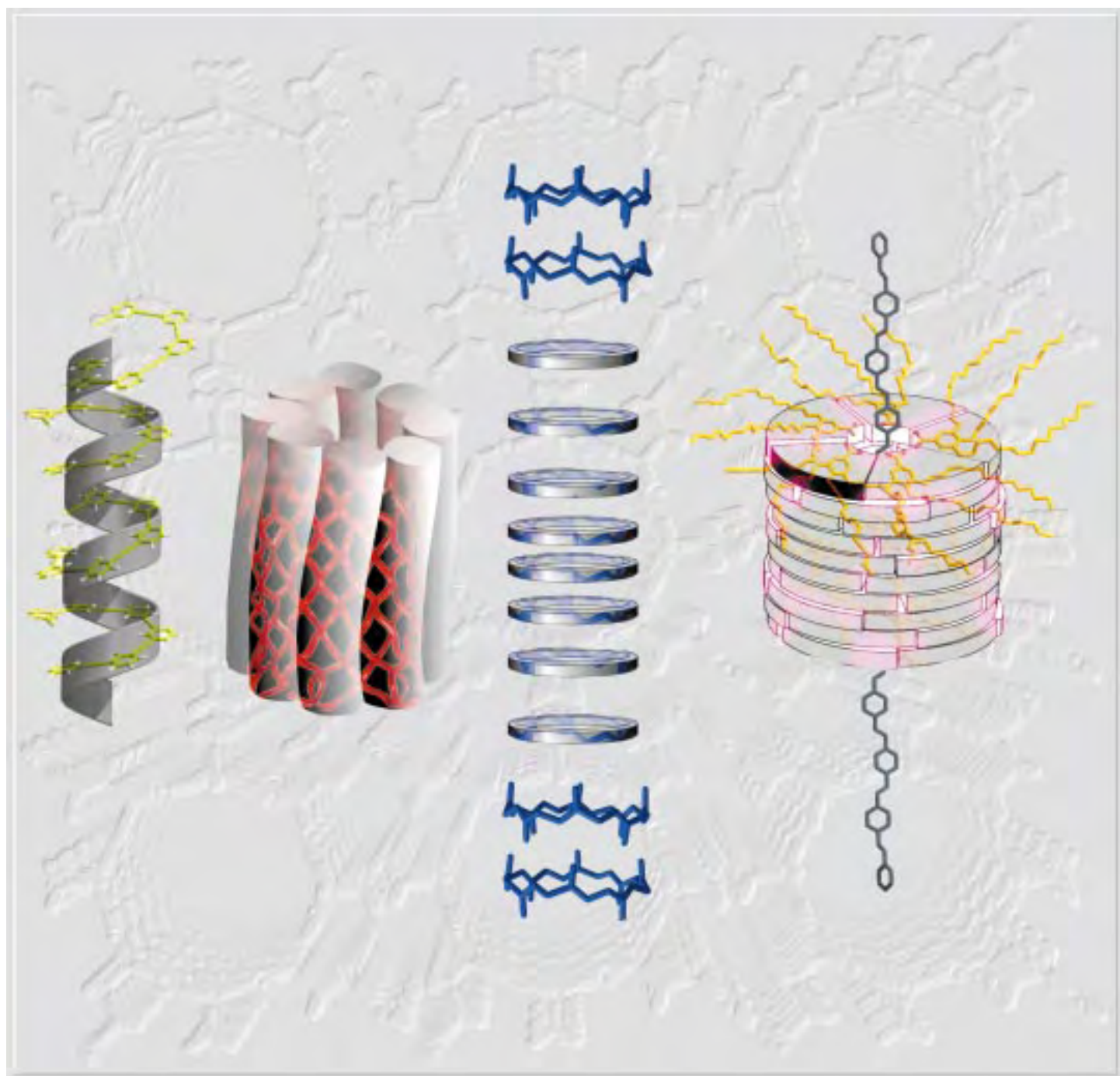
CORRIGENDA

In the Communication by **S. Bobev** and **S. C. Sevov** in Issue 22, 2000, pp. 4108–4110 the references to the discovery (J. D. Corbett, *Inorg. Nucl. Chem. Lett.* **1967**, 3, 173 and *Inorg. Chem.* **1968**, 7, 1980) and the early characterization of Bi_8^{2+} (B. Krebs et al., *Angew. Chem.* **1982**, 94, 453; *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 445 as well as *Chem. Ber.* **1996**, 129, 1219) were omitted. Bi_8^{2+} , which is isoelectronic and isostructural to Sn_8^{6-} , is also the first square-antiprismatic cluster of eight atoms.

In the Communication by **G. Siuzdak** and **W. H. Benner** et al. in Issue 3, 2001, pp. 541–544 the following information was omitted: The first direct mass measurement of a virus was made with TMV ions using the instrument invented at Berkeley (Fuerstenau et al., US Patent 5770857). Those experiments were reported by Fuerstenau and Benner in a poster entitled “Weighing Intact Virus Particles with a Charge Detection Mass Spectrometer” presented at the “44th ASMS Conference on Mass Spectrometry and Allied Topics, Portland, USA, 1996). Some time later, Siuzdak and co-workers visited Berkeley and obtained the results on the RYMV virus using this same instrument.

The correct ISBN of the Book “Chemistry of Fireworks” by M. S. Russell reviewed in Issue 1, 2001, p. 259 is 0-85404-598-8.

Organic Nanotubes



Self-Assembling Organic Nanotubes

Dennis T. Bong, Thomas D. Clark, Juan R. Granja, and M. Reza Ghadiri*

Hollow tubular structures of molecular dimensions perform diverse biological functions in nature. Examples include scaffolding and packaging roles played by cytoskeletal microtubules and viral coat proteins, respectively, as well as the chemical transport and screening activities of membrane channels. In the preparation of such tubular assemblies,

biological systems make extensive use of self-assembling and self-organizing strategies. Owing to numerous potential applications in areas such as chemistry, biology, and materials science considerable effort has recently been devoted to preparation of artificial nanotubular structures. This article reviews design principles and the prepa-

ration of synthetic organic nanotubes, with special emphasis on noncovalent processes such as self-assembly and self-organization.

Keywords: crystal engineering • materials science • nanotubes • self-assembly • sensors

1. Introduction

Organic tubular assemblies are of interest due to their numerous possible applications, many of which are evident from a consideration of biological systems. For example, hollow tubular structures act as conduits of chemical information in the form of transmembrane ion channels^[1] and provide closed reaction chambers, as demonstrated by protein-folding chaperonins^[2, 3] and protein-degradation enzymes.^[4, 5] The cylindrical internal surfaces of these protein compartments are well suited for the presentation of chemical functionality, thus enhancing enzyme activity through functional-group complementarity and chemical catalysis. Furthermore, the bounded nature of the cylinder allows selectivity on the basis of substrate size. The membrane protein aquaporin provides a striking demonstration, as it transports

only water through its central pore and discriminates against all other small polar molecules.^[6]

Inspired by the remarkable functions of tubular structures in biology, much research has focussed on the construction of simpler synthetic tubes for application as specific ion sensors, easily tailored molecular reaction vessels, molecular sieves, or nanoscale fluidic transport systems. An equally intense effort has aimed to apply biologically derived design principles to the construction of functional tubular materials with no known biological analogue. Examples include liquid crystal display components and birefringent materials. While many advances have been reported regarding porous inorganic materials and carbon nanotubes, this review will center on the contributions made by synthetic and bioorganic chemistry to the preparation of tubular constructs. Special attention will be given to noncovalent processes as these strategies possess several inherent advantages over covalent syntheses, the most noteworthy of which include high synthetic convergence, built-in error-correction, control of assembly through subunit design, and overall high efficiency.^[7, 8]

2. Motifs of Tubular Assembly

Conceptually, there are several possible ways to design open-ended hollow tubular structures (Figure 1). For example, a two-dimensional sheet-like starting material can be either rolled or sealed at opposing edges to yield a tube-shaped construct. Such processes have been noted in formation of carbon nanotubes from graphite.^[9, 10] Emulsion-templated mineralization or polymerization is another approach which has proven to be of exceptional utility in the

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preparation of porous silicates and related mesoporous materials.^[11–14] Hollow structures can also be formed by assembly of stave or rod-like subunits into barrel or bundle-shaped frameworks. Examples of this motif include trans-membrane pores formed by β -barrel proteins such as α -hemolysin^[15] and porins,^[16–18] as well as α -helical bundles of cholera toxin^[19] and the potassium channel.^[20] Linear precursors can form tubular structures by coiling into hollow, helical conformations. This motif is illustrated by β -helical structures formed by the natural antibiotic gramicidin A.^[21]

Finally, tubular arrays can be prepared from the stacking of disc or sector-shaped subunits. Self-assembly of the tobacco mosaic virus (TMV) coat protein is perhaps the best known biological instance of this motif.^[22, 24, 25] Of these various approaches, the last three have thus far offered the most design flexibility and synthetic convergence. As detailed in the following sections, most approaches towards tubular constructs have been biomimetic; in general, the self-assembly strategies have resonance with those found in biological systems.



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Dennis T. Bong was born in Victoria, Canada, in 1974. He received his BSc in chemistry from the University of California, Berkeley, in 1994. During his stay at Berkeley, he also received his initiation in chemical research under the guidance of Professor K. Peter C. Vollhardt, studying the physical organic chemistry of strained aromatic systems. From Berkeley he moved to La Jolla, California, to join the chemistry graduate program at the Scripps Research Institute where he is currently completing his PhD work in membrane biophysics, supramolecular chemistry, and de novo protein design under the direction of Professor M. Reza Ghadiri. Research interests in bioorganic chemistry have prompted him to take up a postdoctoral position in the laboratory of Professor Ronald Breslow at Columbia University in New York following the closure of his PhD studies.

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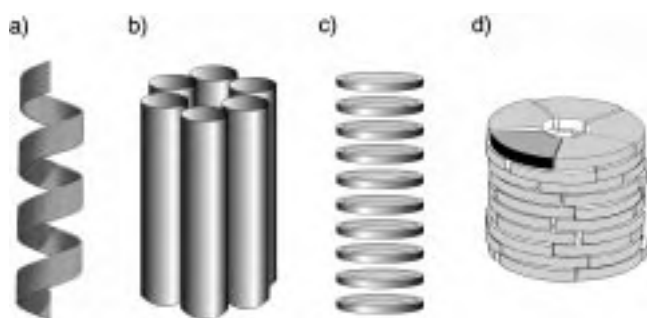


Figure 1. Four possible strategies for the molecular assembly of tubular materials. a) Helical molecules can be coiled to form hollow, folded structures, b) rod-like molecules can be assembled in a barrel-stave fashion to form molecular bundles, c) macrocycles can be stacked to form continuous tubes, and d) sector or wedge-shaped molecules can assemble into discs that subsequently stack to form continuous cylinders, similar to macrocycles.

3. Hollow Coiled Molecules

3.1. Linear D,L-Peptides Form Cylindrical β - or π_{DL} -Helices

The β - or π_{DL} -helices are peptide supersecondary structural motifs in which the backbone folds into a helical conformation stabilized by β -sheet-type hydrogen bonding. First proposed in 1971 by Urry and independently by Ramachandran and Chandrasekaran in 1972, β -helical conformations are common in linear peptides composed of alternating D- and L- α -amino acids (D,L-peptides) due to the conformational requirements for β -sheet hydrogen bonding.^[26, 27] As noted initially by Pauling and Corey, residues in extended sheets must assume pleated conformations in order to alleviate side chain to side chain steric clashes that would result if the residues adopted a fully extended conformation.^[28] For an idealized β -strand composed of all L-amino acids ($C\alpha-N$ torsion angle $\phi_L = -120^\circ$, $C\alpha-C$ torsion angle $\psi_L = 120^\circ$), the pleating of adjacent residues causes the direction of the peptide backbone to alternate in sinusoidal fashion (Figure 2a). Inverting the chirality (L $\rightarrow$ D) of a single residue while maintaining a pleated conformation also requires inverting its backbone dihedral angles ($\phi_D = 120^\circ$, $\psi_D = -120^\circ$), since equivalent conformations of L- and D-residues are related by a factor of -1 .^[27, 29] The direction of pleating in the D-residue reinforces that of the adjacent L-residues and gives rise to an overall bend; inverting the chirality and dihedral angles of every second residue causes the backbone to bend continuously (Figure 2b, c). The peptide can now conveniently satisfy its hydrogen-bonding requirements by adopting a helical conformation (Figure 2d) with quasi-equivalent conformations of L- and D-residues ($\phi_L = -133^\circ$, $\psi_L = 117^\circ$; $\phi_D = 118^\circ$, $\psi_D = -130^\circ$).^[29] Such an idealized β -helix displays screw axis symmetry with a repeat unit of two residues.

While monomeric β -helices necessarily exhibit parallel β -sheet hydrogen bonding, entwined double-stranded parallel ($\uparrow\uparrow$) and antiparallel ($\uparrow\downarrow$) helices are also possible.^[30] β -helices can exist in either right- or left-handed conformations depending on peptide length, residue composition, and prevailing chirality.^[27, 30] In all such structures, amino acid

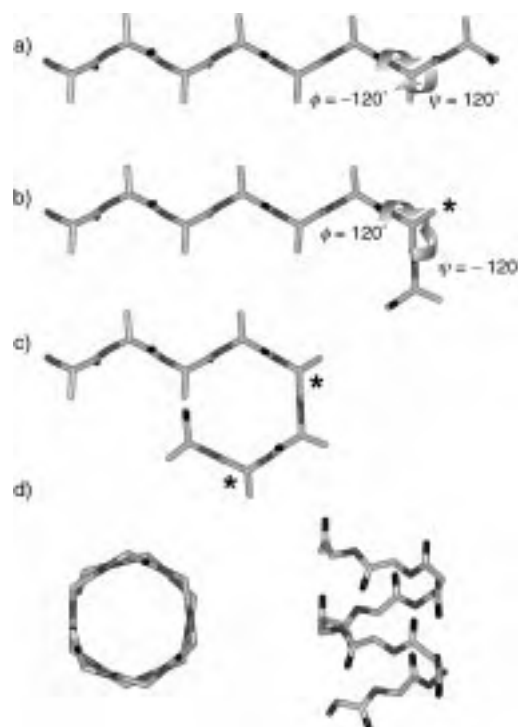


Figure 2. The relationship between the conformation of a β -pleated strand and that of a β -helix. a) An all-L peptide in an idealized pleated β -conformation ($\phi = -120^\circ$, $\psi = 120^\circ$) viewed parallel to the plane of the backbone amide groups (for clarity only the backbone and C_β atoms are shown). b) The chirality of the residue marked with an asterisk has been inverted from L to D. In order to maintain a pleated conformation capable of participating in β -type hydrogen bonding, the backbone dihedral angles of this residue must also be inverted ($\phi = 120^\circ$, $\psi = -120^\circ$). This causes a kink in the peptide chain. c) Inversion of the chirality and backbone dihedral angles of another residue one removed from the first gives rise to a loop in the peptide chain. d) Performing these operations on every second residue causes the peptide chain to bend continuously and form a β -helix. On the left, the β -helix is viewed parallel to the helix axis, emphasizing its internal pore 3.3 Å in diameter. On the right the β -helix is viewed perpendicular to its helical axis in order to illustrate its intrachain β -type hydrogen-bonding pattern. For clarity only the backbone atoms are shown.

side chains radiate outward, leaving an unoccluded central pore running the length of the helix axis. The average radius of the β -helix pore depends upon the helix periodicity, or number of residues per turn (expressed as a superscript; for example, $\beta^{5.6}$ signifies a β -helix with 5.6 residues per turn), with larger periodicities giving rise to larger pores. In principle, helix periodicity can be controlled by varying the backbone hydrogen-bonding register, making β -helices potentially attractive scaffolds for preparation of tubular structures with tailored internal dimensions.^[27, 29] Indeed, computational studies have indicated that single-stranded β -helices with 4.8, 6.2, and 8.2 residues per turn should display pore diameters of 2.3, 3.3, and 4.7 Å, respectively.^[29]

Interest in β -helical structures can be traced to a 1941 report describing isolation and partial characterization of a mixture of *Bacillus brevis* peptide antibiotics known collectively as gramicidin.^[31] Degradation studies revealed that the major constituent, named gramicidin A, is a linear penta-decapeptide composed of alternating D- and L-amino acids with the following primary structure: HCO-L-Val-Gly-L-Ala-

D-Leu-L-Ala-D-Val-L-Val-D-Val-L-Trp-D-Leu-L-Trp-D-Leu-L-Trp-NHCH₂CH₂OH.^[32–35] Recognition of the transmembrane pore-forming ability of gramicidin A^[36] led to a number of proposed models for the active species. Based on conformational analysis, in 1971 Urry put forth a structure in which the molecule adopts β -sheet-type torsion angles, with the alternating chirality of adjacent residues giving rise to helical curvature reinforced by interresidue hydrogen bonding.^[26] The dependence of equilibrium conductance on antibiotic concentration,^[37] coupled with the requirement that the active form of gramicidin A be of sufficient length to span a lipid bilayer wider than 35 Å, prompted Urry to suggest a dimeric structure in which two single β -helices associate in a head-to-head fashion through backbone–backbone hydrogen bonding.^[26] Recent solid-state NMR spectroscopy work in a lipid medium has confirmed the essential features of this model.^[21]

Early studies of synthetic β -helices focused on syndiotactic homopolydipeptides.^[38, 39] In particular, X-ray and electron fiber diffraction studies of poly- γ -benzyl-D,L-glutamate demonstrated that the polymer can exist in not only single- but also double-stranded β -helical conformations.^[40, 41] While double- or higher stranded helical structures had long been known for polynucleotides and certain polysaccharides, these were the first such structures documented for polypeptides. The periodicity of β -helices obtained in crystalline samples ranged from 5.6 to 10.9 residues per turn and was found to be highly dependent on the crystallization solvent. These observations were rationalized in terms of expansion or contraction of the helical pore to accommodate included solvent molecules.^[41]

In 1975 DeSantis and co-workers reported the first attempts at preparing β -helix-forming oligopeptides of discrete length.^[39] In the solid state, peptides of general sequence X(L-Ala-D-Val)_mY displayed X-ray powder diffraction patterns consistent with α -pleated structures^[28, 29, 42] while circular dichroism (CD) spectra of the polymer in trifluoroethanol (TFE) suggested a β -helical conformation. In addition, ¹H NMR spectra ([D₆]DMSO) of hexa- and octapeptides (X = benzyloxycarbonyl (Cbz), Y = OMe) were well dispersed and showed ³J_{NH,αH} values of nearly 8.5 Hz, which strongly evince β -type ϕ torsion angles.

In 1979 an X-ray crystallographic study of octapeptide Boc-(L-Val-D-Val)₄-OMe (Boc = *tert*-butoxycarbonyl) by Lorenzi and co-workers provided the first atomic resolution structure of a β -helical peptide.^[43, 44] The compound crystallized as a C₂-symmetrical left-handed double $\beta^{5,6}$ -helix. Later NMR studies supported the existence of similar left-handed double helical structures in solution.^[45–47] Related higher homologues were found to exist predominantly as a mixture of monomeric left- and right-handed $\beta^{4,4}$ -helices, presumably due to an increased opportunity for intramolecular hydrogen bonding as compared with the octapeptide.^[48–50] Lorenzi and co-workers also observed gramicidin-like head-to-head dimerization of monomeric $\beta^{4,4}$ -helices formed by *N*-formylated nonapeptide HCO-L-Ile-(D-allo-L-Ile)₄-OMe^[51] (allo = allo-isoleucine), as well as tetramerization of heptapeptide HCO-L-Phe-(D-Phe-L-Phe)₄-OMe to give an unusual head-to-head dimer of double-stranded $\uparrow\uparrow\beta^{5,6}$ -helices.^[52]

Mirroring the findings with other β -sheet model systems,^[53–55] Lorenzi and co-workers indicated that linear stereocooligopeptides (that is, peptides of alternating D,L-configuration) containing β - or γ -branched side chains strongly favor β -helical conformations.^[56] In contrast, the less sterically demanding syndiotactic oligonorleucines between 8 and 15 residues in length did not form β -helices and proved much less soluble in chloroform than related branched species.^[57] The reduced steric bulk presumably results in a lesser degree of β -helical preorganization in the backbone, allowing precipitation through the formation of α -pleated-sheet aggregates.^[28, 29, 42] Introduction of a single backbone *N*-methyl substituent at the (*n* – 3)-position abolished higher order aggregation and led to a mixture of soluble single-stranded $\beta^{4,4}$ - and double-stranded $\uparrow\downarrow\beta^{5,6}$ -helices.^[57] The foregoing studies underscore the strong influence of solvent, peptide length, amino acid composition, and terminating groups on β -helical structures, all of which complicate prediction of the pore size. In addition to a variety of β -helical structures, linear D,L-peptides are also capable of adopting α -helical and α -pleated-sheet conformations.^[58] The conformational promiscuity of these structures, though informative, may undercut their utility in certain applications. It is possible that the membrane-spanning requirement imposed on gramicidin A limits the number of accessible conformations, thus contributing to its reliable formation of the head-to-head dimer in the membrane. Indeed, X-ray crystallographic studies have revealed that gramicidin A can adopt several different conformations in the solid state, depending upon crystallization conditions and the identity of any additives present.^[59–66] However, it is expected that many D,L-peptides of non-gramicidin A sequence would display membrane and possible antibiotic activity,^[67] since membrane insertion should be governed primarily by side-chain hydrophobicity.^[68]

3.2. Helical Folding of Linear Oligophenylacetylenes

Moore, Wolynes, and co-workers have described folding of nonbiopolymers: oligophenylacetylenes can fold into helical conformations.^[69] The design takes advantage of Moore's "shape-persistent" approach to nanoscale architectures in which *n* rigid phenylacetylene subunits are coupled together with a *meta* relationship (Figure 3), and thus nucleate helix-turn conformations within the resulting oligomer.^[70] A helical conformer could be stabilized by solvophobic-driven packing between backbone phenyl rings. Moore reasoned that these interactions would favor self-organization of linear oligomers into folded helical conformations. The relatively wide angle of the turn (approximately 120°) prevents a close-packed core, resulting in a hollow coil reminiscent of peptide β -helices. The spontaneous folding of this linear synthetic polymer into a compact, defined shape places oligophenylacetylenes into the growing family of molecules known as "foldamers".^[71–73]

Linear oligophenylacetylenes with the general structure shown in Figure 3 were studied by UV and NMR spectroscopy. In chloroform solution, Moore and co-workers found

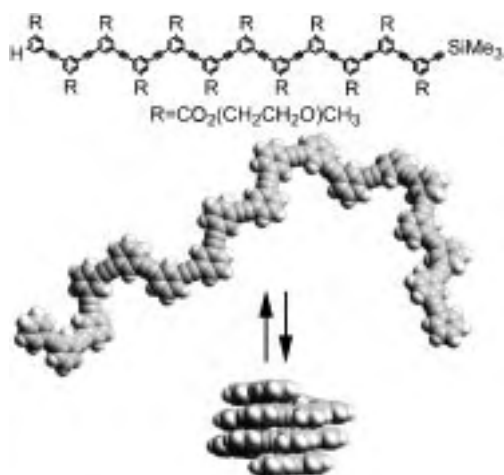


Figure 3. Oligophenylacetylene folding equilibrium between the open state and the helical folded structure (space-filling representation). The ester substituents on each phenyl ring have been omitted in the space-filling model for clarity.^[70] Reprinted with permission from ref. [74]. Copyright (2000) American Chemical Society.

the molar extinction coefficient at 303 nm showed a linear dependence on the length of the molecule. However, in acetonitrile the length dependence was biphasic; compounds with $n > 8$ displayed, per molar phenylacetylene subunit, ϵ_{303} values 35 % smaller than shorter oligomers. This decrease in absorbance was found to be concentration independent, which rules out intermolecular associations, and was attributed to hypochromic effects arising from intramolecular association of aromatic groups. In ^1H NMR spectroscopic experiments, average chemical shifts of aromatic protons were dramatically upfield shifted for $n > 8$, consistent with magnetic shielding due to aromatic π -stacking interactions. The helical nature of these foldamers was assessed by CD studies. As expected, the oligophenylacetylene alone in acetonitrile–water mixtures displays no detectable Cotton effect, since the polymer should exist as a helical racemate. However, when a chiral guest such as α -pinene is added, a clear CD signature is observed in the phenylacetylene absorption region; further, (+)- α -pinene and (–)- α -pinene induce equal and opposite CD spectra (Figure 4).^[74] Binding analyses indicated a 1:1 stoichiometry of association, which suggests binding to the internal hydrophobic pore surface rather than to the outer polar surface. Similar twist-sense bias has been induced in these oligomers by incorporation of a chiral center on the ethylene glycol side chain,^[75] as well as incorporation of an enantiopure binaphthol unit into the phenylacetylene backbone.^[76] Additional support for the formation of a tubular cavity was provided by studies in which a nitrile functionality was incorporated on every other phenyl ring of the dodecamer, *ortho* to both phenylacetylene linkages. This should result in the formation of one trigonal planar metal-binding site per helical turn, which modeling indicated would require six phenylacetylene subunits. Indeed, UV titration studies with AgO_3SCF_3 and electrospray mass spectroscopy revealed a 2:1 stoichiometry of Ag–oligomer binding, to support the notion that helical folding of the oligophenylacetylene occurs with the formation of a tubular cavity which is approximately 4 Å in diameter.^[77]

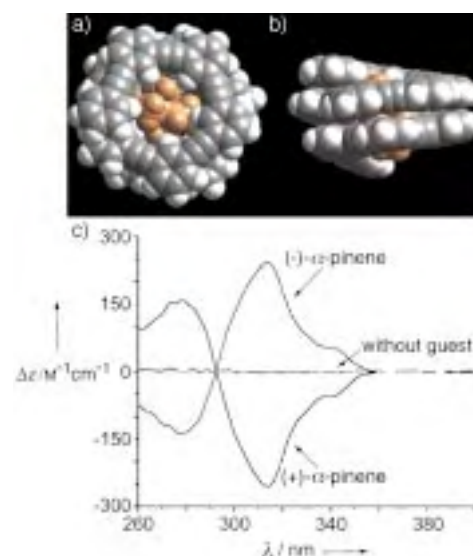


Figure 4. Space-filling model of the oligophenylacetylene shown in Figure 3 coiled around α -pinene: viewed (a) along helical axis and (b) orthogonal to the helical axis.^[74] c) Overlaid CD spectra in acetonitrile/water (60/40). Both the oligophenylacetylene (4.2 μm) and (–)- α -pinene (420 μm) display negligible CD signatures. However, when the two are mixed, a strong positive Cotton effect is observed at 314 nm. The mirror image spectrum is obtained with the oligophenylacetylene and the opposite enantiomer, (+)- α -pinene. Reprinted with permission from ref. [74]. Copyright (2000) American Chemical Society.

Given the facile solid-phase methods for oligophenylacetylene synthesis,^[78] additional interesting derivatives should be readily available to provide further insight into this intriguing system.

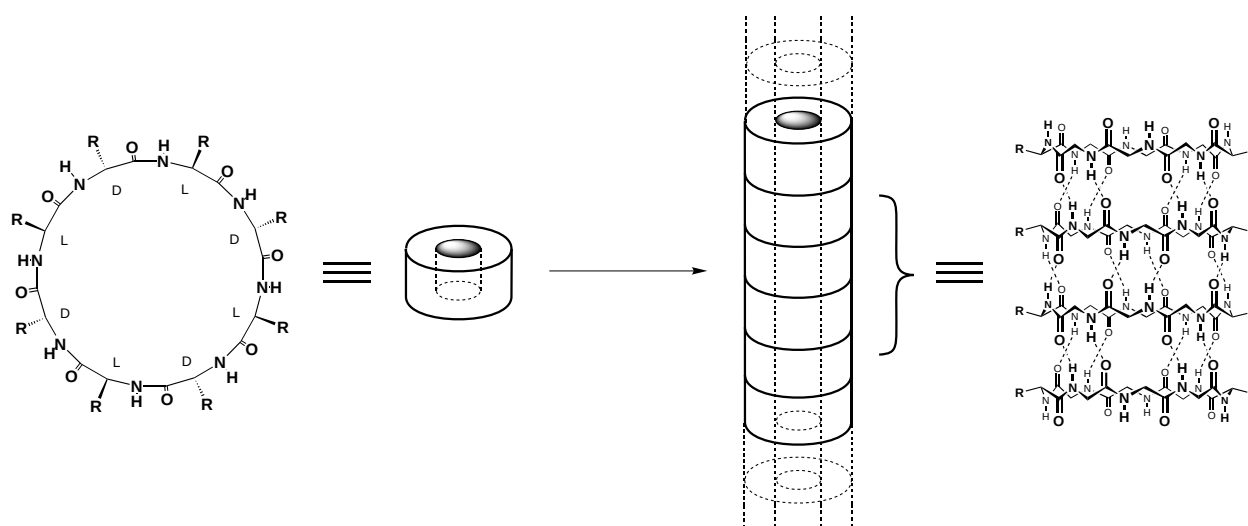
4. Ring-Stacking Motifs

4.1. Tubular Ensembles from Cyclic D,L- α -Peptides

4.1.1. Microcrystalline Peptide Nanotubes

Within the context of a theoretical analysis of regular enantiomeric peptide sequences, in 1974 DeSantis et al. recognized that peptides comprised of an even number of alternating D- and L-amino acids displaying conformationally equivalent β -type dihedral angles would form closed rings capable of stacking through backbone–backbone hydrogen bonding.^[29] The resulting hollow cylindrical ensembles are conceptually related to the β -helical conformations adopted by linear D,L-peptides (Figure 2).^[79–82] Initial attempts to experimentally demonstrate this type of tubular construct proved inconclusive.^[83] In 1989 an X-ray crystallographic study by Lorenzi and co-workers on the hexapeptides *cyclo*[-(L-Phe-D-Phe)₃-] and *cyclo*[-(L-Val-D-Val)₃-] revealed that the expected intersubunit associations were absent and each peptide was found instead to be tightly hydrogen bonded to several cocrystallized solvent molecules.^[84]

In 1993 our laboratory compellingly demonstrated the formation of hollow tubular structures by the stacking of cyclic D,L-peptide rings (Scheme 1).^[85] The sequence of octapeptide *cyclo*[-(L-Gln-D-Ala-L-Glu-D-Ala)₂-] was chosen to impart solubility in basic aqueous solution, and thereby to prevent subunit association through coulombic repulsion.



Scheme 1. Schematic diagram of nanotube assembly from cyclic D,L-peptides. For clarity, most of the peptide side-chains have been omitted.

Controlled acidification produced microcrystalline aggregates with high aspect ratios (length/thickness; Figure 5) that were examined by electron microscopy, electron diffraction,



Figure 5. Phase-contrast microscopy images of cyclic D,L-peptide nanotube microcrystals.

FT-IR spectroscopy, and crystal structure modeling. These analyses convincingly established the expected structure in which the ring-shaped subunits stack through antiparallel β -sheet hydrogen bonding to form hollow tubes with a van der Waals internal diameter of approximately 7 Å. Lambert and co-workers recently employed a similar pH-controlled assembly strategy to prepare microcrystals of a cyclic D,L-octapeptide containing bis-aspartic acid.^[86] The IR spectrum and morphology of the crystals formed by *cyclo*[-(L-Asn-D-Phe-L-Asp-D-Phe)₂-] were similar to those of *cyclo*[-(L-Gln-D-Ala-L-Glu-D-Ala)₂-] described earlier, which strongly suggests a tubular structure for this peptide.

One advantage of cyclic D,L-peptide nanotubes with respect to their β -helical counterparts is the possibility of rigorously controlling the internal diameter of the nanotube by simply varying the size of the peptide ring. A 1994 report from our laboratory demonstrated this design flexibility. The dodecapeptide *cyclo*[-(L-Gln-D-Ala-L-Glu-D-Ala)_n-] ($n=3$) was shown to undergo proton-triggered assembly in a manner

analogous to that previously described for its lower homologue ($n=2$).^[87] The resulting microcrystalline aggregates display an expanded van der Waals internal diameter of 13 Å.

Our laboratory has also prepared solid-state nanotubular assemblies using several uncharged cyclic octapeptides.^[88] For all cases reported from this laboratory, unit cell parameters obtained from cryoelectron microscopy and electron diffraction analyses are fully in accord with the expected tubular structures (Figure 6). Observed intersubunit distances of 4.8 Å strongly evince the anticipated β -sheet structures; furthermore, FT-IR spectroscopic studies reveal amide I_⊥, amide I_{||}, amide II_{||}, and hydrogen-bonded amide A bands which are characteristic of an antiparallel β -sheet arrangement. The low solubility of the cyclic D,L-peptide subunits and high stability of the resulting aggregates suggests significant preorganization of the monomeric units and a strongly cooperative assembly process. Recently, Karlström and Udén have explored association of cyclic D,L-octapeptides in water using a fluorescence-quenching assay. Their data indicate detectable intersubunit hydrogen bonding even in the strongly competing aqueous medium.^[89]

4.1.2. Self-Assembling Transmembrane Ion Channels and Pore Structures from Cyclic D,L- α -Peptides

A noteworthy feature of cyclic D,L-peptide nanotubes is the ease with which the external surface properties and internal diameter of the tubular ensemble may be altered through appropriate choice of amino acid side chains and the size of the peptide ring, respectively. For instance, in the design of transmembrane channels the ability to match the surface characteristics of nanotubes to the physical properties of the surrounding media proved of paramount importance. It was hypothesized that cyclic D,L-peptides bearing appropriate hydrophobic side chains would partition into nonpolar lipid bilayers and undergo self-assembly. In 1994 our laboratory validated this hypothesis by reporting the first self-assembling transmembrane ion channels based on the cyclic D,L-peptide nanotube framework (Figure 7).^[90] Since then several other

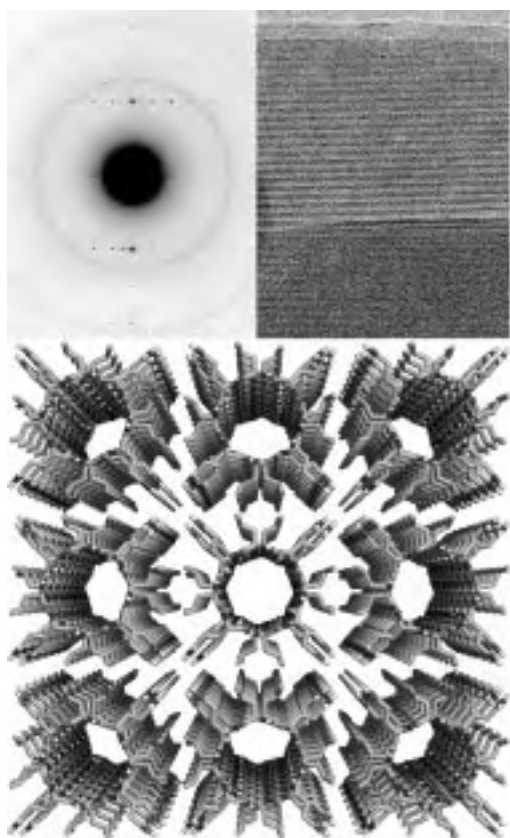


Figure 6. Bottom: Crystal-structure model calculated from electron microscopy for a cyclic D,L-peptide; nanotubular organization can be clearly seen. Top left: The corresponding electron diffraction pattern. Top right: A low-dose cryo-electron micrograph of the peptide microcrystals. Striations in the cryo-TEM image are approximately 18 Å apart; this corresponds to the diameter of a cyclic D,L-octapeptide and indicates side-by-side packing of the nanotubes in the solid state.^[85]

cyclic octapeptides have been examined by fluorescence proton-transport assays and single-channel conductance measurements.^[91] The self-assembling ion channels display transport activities for K^+ and Na^+ greater than 10^7 ions s^{-1} , rivaling the activity of the related natural product gramicidin A (Figure 7). More recently, grazing-angle reflection/absorption, polarized attenuated total reflectance (ATR), and transmission Fourier transform infrared (FT-IR) spectroscopic analysis of complexes formed from multiple lipid bilayers and peptides have shown that the nanotubes orient themselves nearly parallel to the lipid acyl chains, which supports our model of the peptide nanotubes as the active channel species.^[92]

As noted above, an important feature of cyclic D,L-peptide nanotubes is the ability to control the internal diameter by varying the ring size of the peptide subunit. Modeling studies suggested that subunits comprised of ten or more residues would form transmembrane pores large enough to mediate transport of small hydrophilic molecules across lipid bilayers. Consistent with these expectations, decapeptide *cyclo*[-(L-Trp-D-Leu)_n-L-Gln-D-Leu-] ($n=4$), which possesses a van der Waals internal diameter of 10 Å, displays efficient glucose transport activity, while its smaller octapeptide counterpart ($n=3$, internal diameter approximately 7 Å) lacks such

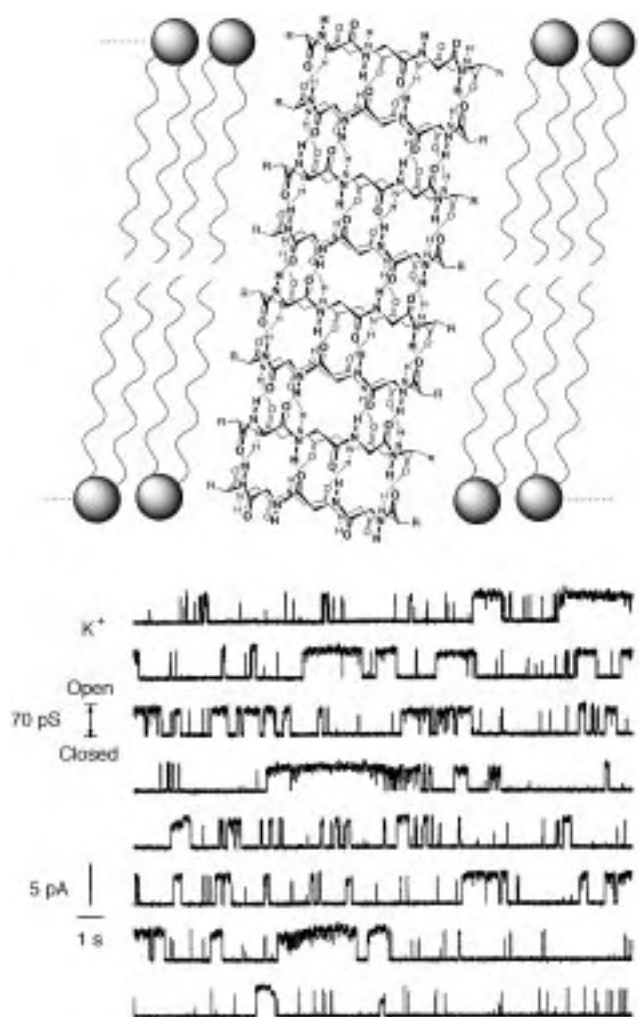


Figure 7. Top: Schematic representation of cyclic D,L-peptides assembled as a transmembrane channel. The off-normal tilt of the lipids and the peptide assembly are based on orientation studies using dichroic ATR-IR (ATR = attenuated total reflection).^[92] Bottom: Ionic conductance induced by the insertion of cyclic D,L-peptides into a voltage-clamped membrane.^[90]

activity.^[93] These findings suggest that even larger cyclic peptide subunits may prove useful in the delivery of pharmacologically active agents.

Cyclic D,L-octapeptide transmembrane channels have also been examined using computational methods. A model transmembrane channel structure was studied in our laboratory using molecular dynamics simulations. These results suggest that ordering of water molecules inside the channel lumen may be responsible for the observed high rates of ion transport (Figure 8).^[94] Using an Ohmic model of channel conductance together with an empirically derived correction factor, Smart and co-workers found that the observed channel conductance for *cyclo*[-(L-Trp-D-Leu)₃-L-Gln-D-Leu-] correlates well with the expected pore size.^[95] Based on Connolly surface-type calculations using the program HOLE, these authors reported a minimum internal diameter of 4.96 Å for the pore formed by the cyclic octapeptide, a result that contrasts with the 7 Å value reported earlier from our laboratory^[90] but that corresponds well with the anticipated 4.7 Å internal diameter of the related $\beta^{8.2}$ -helical structure.^[29] The discrepancy arises because the 7 Å value is derived from



Figure 8. Snapshot of a 0.76-ns molecular dynamics simulation of a stack of ten cyclic D,L-peptides in water.^[94] A section through the tube is shown, to reveal the relative organization of internal waters. Four types of orchestrated water movements were observed during the simulation that may contribute to the observed high rates of transport.

van der Waals rather than Connolly surface calculations; thus 4.96 Å and 7 Å probably represent the approximate minimum and maximum pore sizes, respectively.

4.1.2. Solution-Phase Tubular Assemblies from Cyclic D,L- α -Peptides

The fundamental translational repeat unit of cyclic D,L-peptide nanotubes comprises two subunits associated through antiparallel β -sheet hydrogen bonding. This minimal motif has been studied with the aid of selective backbone *N*-alkylation, which blocks one face of the peptide ring. In 1994 an X-ray crystallographic study of hemi-*N*-methylated hexapeptide *cyclo*[(*L*-^{Me}N-Leu-D-Leu)₃] by Lorenzi and co-workers provided the first atomic resolution information regarding cyclic D,L-peptide nanotube structure.^[96] This compound was shown to adopt the expected dimeric antiparallel β -sheet structure in the solid state, while NMR investigations revealed that the peptide dimerizes in deuterochloroform with an association constant of 80 M⁻¹.^[97] Independent work carried out in our laboratory demonstrated analogous solution and solid state dimerization by octapeptide *cyclo*[(*L*-Phe-D-^{Me}N-Ala)₄] (Figure 9).^[98] A recent study has examined the dimerization



Figure 9. Structure of a cyclic D,L-peptide (*cyclo*[(*L*-Phe-D-^{Me}N-Ala)₄]) in the crystal form (top and side views). This peptide is limited to dimer formation by *N*-alkylation of alternate amides.^[98] Alkylation prevents further oligomerization driven by hydrogen bonding. The cylindrical cavity is filled with partially disordered water molecules.

of twenty cyclic D,L- α -peptides varying in location and identity of backbone alkyl substituents, amino acid composition, and ring size.^[55] Our findings establish that, of the various ring sizes examined, cyclic octapeptides exhibit optimal rigidity and predisposition for nanotube assembly. A variety of *N*-alkyl substituents were tolerated, for example, methyl, allyl, *n*-propyl, and pent-4-en-1-yl groups. In addition, initial

findings suggest that residues with γ -branched side chains favor dimerization over those with unbranched side chains, presumably by predisposing the peptide backbone for β -sheet formation.

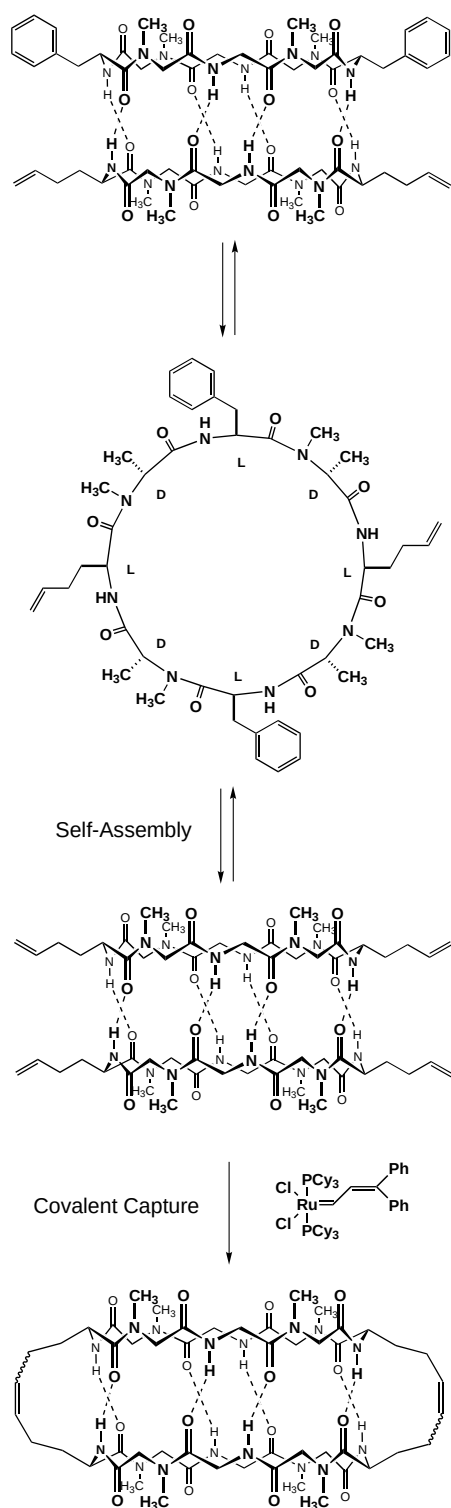
Self-assembling peptide cylinders have also provided the first experimental model system for assessment of the relative stability of parallel and antiparallel β -sheet structures.^[99] Measurement of solution equilibrium constants revealed that antiparallel orientation is favored over parallel by 0.8 kcal mol⁻¹. Results from independent computational studies corroborate these findings.^[100, 101]

In model studies directed toward preparation of polymeric tubular biomaterials, the feasibility of covalently capturing noncovalent cyclic peptide dimers has been examined. Octapeptide *cyclo*[(*L*-Phe-D-^{Me}N-Ala-L-Hag-D-^{Me}N-Ala)₂] bearing two olefin groups underwent selective olefin metathesis mediated by hydrogen bonds to yield the corresponding covalently tethered β -sheet peptide dimer (Scheme 2).^[102] Recent work has employed disulfide isomerization to extend the scope of this general strategy.^[103] In the two peptide systems examined, intersubunit hydrogen bonding serves important yet distinct functions. In the case of olefin metathesis, hydrogen bonding appears to drive the reaction by increasing local concentration of olefin functionalities. In contrast, for disulfide isomerization, hydrogen bonding appears to control partitioning between two alternative disulfide-bonded dimers by contributing to the stability of the hydrogen-bonded isomer. Our proposed mechanism (Scheme 3) for the latter transformation is reminiscent both of thiol-catalyzed “unscrambling” of RNase A and oxidative refolding pathways of natural proteins and protein fragments.

4.2. Tubular Ensembles from Cyclic Peptides Containing β -Amino Acids

In 1972 Hassall hypothesized that cyclic tetramers of alternating α - and β -amino acids would assemble through backbone–backbone hydrogen bonding to yield hollow cylindrical constructs.^[104] A crystallographic study of tetrapeptide *cyclo*[(*L*-Ser(*Or*Bu)- β -Ala-Gly- β -Asp(OMe))₄] in 1974 only partially validated this proposal.^[105] The peptide subunits adopted a ring-shaped conformation and stacked above one another in the crystal lattice; however, only two of the four amide groups participated in expected intersubunit hydrogen bonding.

While the design of tubular assemblies employing mixed α - and β -amino acid cyclic peptides awaits definitive demonstration, cyclic peptides composed of all β -amino acids have already found application in preparation of hollow tubular assemblies.^[106, 107] Seebach and co-workers have reported that cyclic tetrapeptides composed solely of chiral β^3 -amino acids can form hollow tubular structures similar to those displayed by cyclic D,L- α -peptides.^[106] Molecular modeling based on X-ray powder diffraction data has indicated that tetrapeptides *cyclo*[(β^3 -(*S*)-HAla)₄], *cyclo*[(β^3 -(*S*)-HAla- β^3 -(*R*)-HAla)₂], and *cyclo*[(β^3 -(*S*)-HAla)₂-(β^3 -(*R*)-HAla)₂] all exhibit tubular structures in the solid state (Figure 10). Recently our laboratory demonstrated ion channel formation by two cyclic β^3 -



Scheme 2. Schematic illustration of the covalent capture of a cyclic peptide dimer using olefin metathesis. The peptide *cyclo*[-(Phe-D^{Me}N-Ala-Hag-D^{Me}N-Ala)₂-] self-assembles in solution to provide two interconverting dimers in equal proportions (Hag = homoallylglycine). Only the complex in which the homoallyl side-chains are directly across from each other can undergo metathesis to form the covalent product.^[102] Reprinted with permission from ref. [102]. Copyright (1995) American Chemical Society.

tetrapeptides (Figure 11).^[107] Fluorescence proton transport experiments and single-channel conductance data indicate ion-channel activities similar to those of cyclic D,L- α -peptides,

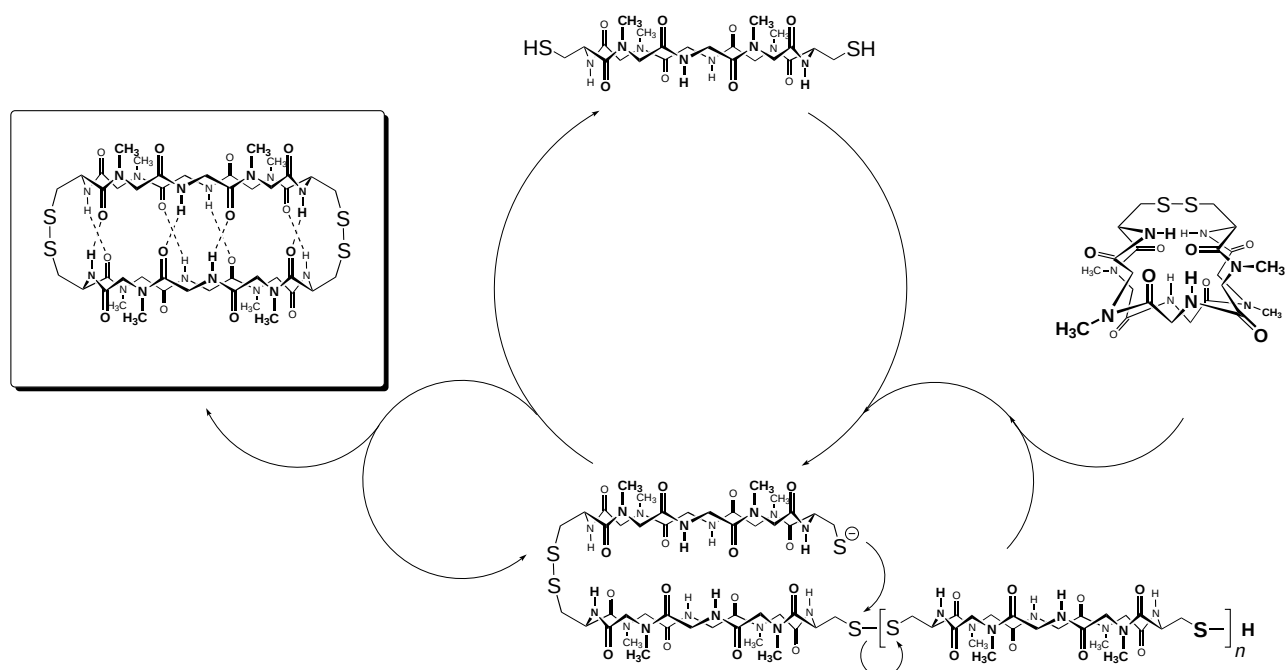
with K⁺ transport rates of 1.9×10^7 ions per second. Channel-forming cyclic β^3 -peptides are also expected to exhibit unique properties distinct from those of their D,L- α -peptide counterparts. For example, the unnatural β^3 -peptide backbone has been shown to cause uniform alignment of amide groups in the solid state structure of *cyclo*[-(β^3 -(S)-HAla)₄-] (Figure 10).^[106] Analogous alignment of amide groups in the proposed channel structures should give rise to a macrodipole moment reminiscent of an α -helix. This dipole is expected to influence the conductance of cyclic β^3 -peptide ion channels by causing voltage gating and current rectification behavior. In contrast, the alternating directionality of amide functionalities in cyclic D,L- α -peptide nanotubes causes local dipole moments to be cancelled out; therefore no voltage gating or current rectification behavior is expected for these channel structures.

4.3. Cystine Macrocycles

The foregoing examples of ring-stacking motifs employ symmetrical cyclic subunits displaying a high degree of self-complementarity due to the formation of multiple noncovalent intermolecular contacts. Ranganathan, Karle et al. have explored the assembly properties of less symmetric macrocycles, and found that very few specific recognition sites are required to induce in-register macrocycle stacking. Their studies have focussed on macrocycles composed of *n*-alkanes (from butyl to decyl) that bridge a cystine moiety either as bisamides^[108] or bisureas.^[109] These compounds were expected to be macrocyclic hosts for lipophilic guests, and indeed, when the bisureas are treated with α,ω -alkane dicarboxylic acids, their chloroform solubility increases dramatically, suggesting that carboxylate recognition disrupts aggregation by inducing urea conformations parallel to the ring plane. This supposition was confirmed by ¹H NMR studies.^[109] Surprisingly, despite the demonstrated conformational flexibility of the macrocycle, these molecules organize in the solid state to form tubular arrays with open molecular pores in which cystines are on one side of the tube and alkane loops form the other side of the tube. The central pores are roughly rectangular and range from 5–10 Å on the long axis and 4–4.5 Å on the shorter axis. Two molecules within a stack are stitched together through two hydrogen bonds in the bisamide and four hydrogen bonds in the bisurea. Additional aggregation free energy probably arises from the hydrophobic collapse of the alkyl region of the tube. As expected, these amphiphilic tubes assemble in the lattice to optimize molecular packing, however, when possible, the hydrophobic side of a single tube is completely buried against other hydrophobic tube faces.

4.4. Serinophanes

Ranganathan et al. have also recently reported studies on an aromatic cyclodepsipeptide based on serine (serinophane), which also stacks to form crystalline cylindrical assemblies.^[110] Interestingly, the amide hydrogen-bonding functionality is directed into the plane of the ring, preventing its participation



Scheme 3. Minimal mechanism for disulfide exchange in *cyclo*[(Phe-D-MeN-Ala-Cys-D-MeN-Ala)₂]. The intramolecular cystine first experiences intermolecular thiol–disulfide exchange to give the linear oligomer. When $n \geq 1$, intramolecular disulfide exchange yields the thermodynamically favored dimeric species.

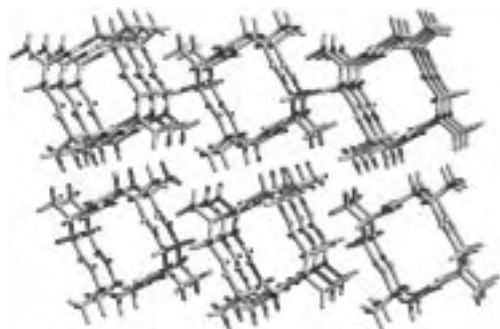


Figure 10. Crystal structure of the cyclic β -peptide, *cyclo*[-(β^3 -(S)-HAla- β^3 -(R)-HAla)₂] that shows the formation of tubular peptide arrays.^[106]

in intermolecular tubular aggregation. Instead, the assembly is driven by aromatic π -stacking of pyridyl and phenyl rings (Figure 12), similar to the phenylacetylene macrocycles (see Section 4.6). However, adjacent rings in a column do not come into direct van der Waals contact; rather, the phenyl rings of surrounding columns interdigitate to form intertubular zipper-like structures. Structural analysis also showed alternation in the stack between phenyl and pyridyl rings. Notably, while the phenyl–pyridyl and dipyril serinophanes formed channel structures, the diphenyl compound did not display π -stacked structures at all, underscoring the subtlety of weak molecular recognition motifs. This aromatic flat-ring peptide system, as well as Moore's phenylacetylene oligomers (see Section 4.6), may well be suitable for exploring other well-defined aromatic interactions, such as phenyl–perfluorophenyl recognition^[111–113] or cation– π -induced stacking.^[114–118]

4.5. Carbohydrate Nanotubes

In 1992 a report by Harada, Li, and Kamachi described preparation of a novel cyclodextrin polyrotaxane by threading a single polyethylene glycol bisamine (PEG-BA) molecule through several cyclodextrins, then stoppering the amine ends with dinitrofluorobenzene.^[119] A later study described an elegant extension of this methodology in which the templated rotaxane assembly was covalently cross-linked using the biselectrophilic reagent epichlorohydrin (Scheme 4).^[120] Subsequent destoppering and purification by gel filtration afforded the polymeric nanotubular structure. The identity of the product was confirmed by NMR, IR, and UV spectroscopies, and by gel filtration analysis. Given the well-known tendency of cyclodextrins to form inclusion complexes, these tubular polymers are expected to exhibit interesting host–guest behavior. Similarly, recent reports have described oligomeric “nanotube” inclusion complexes between cyclodextrins and α,ω -diphenylpolyenes.^[121–123] However, the resulting complex is not stable in the absence of a polyene guest, and are perhaps more properly classified as polypseudorotaxanes.

The polysaccharide backbone itself has inherent conformational preferences, depending on the linkage pattern. This is strikingly demonstrated by the hollow, helical form adopted by α -amylose, which is a regularly repeating polymer of glucose. The curvature of this linear polymer is a direct consequence of the $\alpha(1 \rightarrow 4)$ linkage and results in a helical pore; indeed, iodine stains starch by filling this molecular cavity with iodine.^[124, 125] Employing an efficient polycondensation–cycloglycosylation strategy, Stoddart and co-workers have recently prepared the cyclic variant of coiled oligosaccharides in a series of novel cyclodextrin analogues from

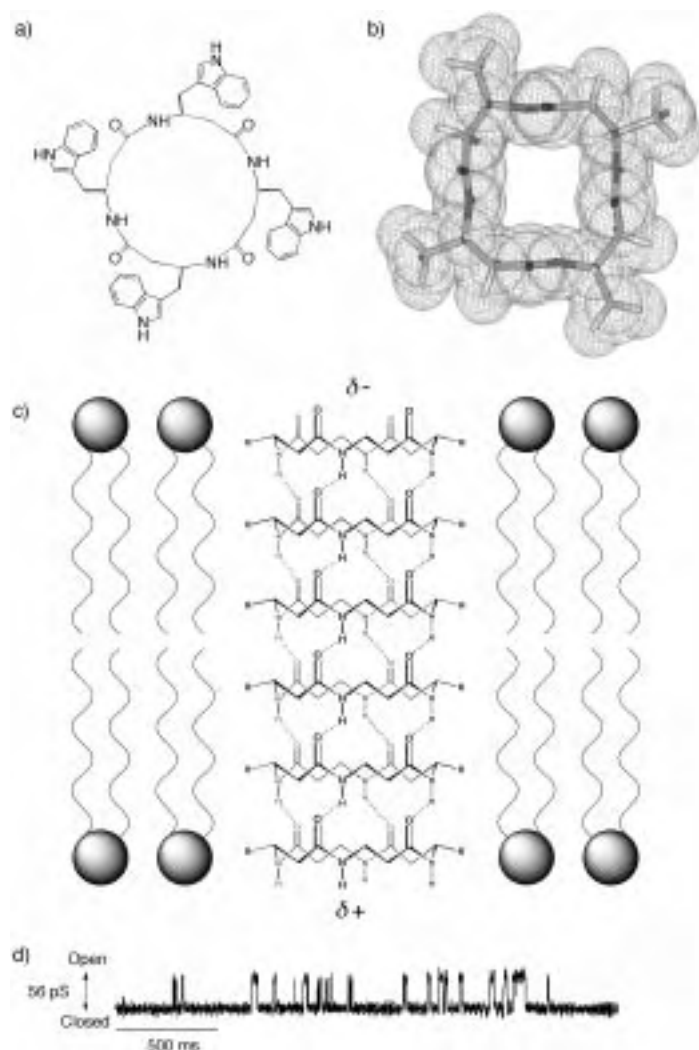


Figure 11. a) Schematic illustration of a cyclic β^3 -tetrapeptide, $\text{cyclo-}[(\beta^3\text{-HTrp})_4]$, designed to form a transmembrane ion channel. b) Molecular model of the channel-forming β^3 -peptide, with surface rendering indicating the 2.6–2.7 Å open pore. c) Illustration of the transmembrane insertion of the cyclic peptide assembly, which displays the expected parallel ring-stacking. d) Single-channel K^+ conductance trace induced by cyclic β^3 -peptide and recorded at 60 mV.^[107] As with the cyclic D,L- α -octapeptides, the opening and closing events may reflect rapid peptide assembly–disassembly events in the membrane.

protected disaccharide precursors.^[126–128] Initial work focused on cyclic (1 $\rightarrow$ 4)- α -linked oligomers of L-rhamnopyranose–(1 $\rightarrow$ 4)- α -D-mannopyranose. Trityl cation catalyzed cyclo-oligomerization of trityl/cyanoethylidene-activated disaccharide followed by deprotection afforded good yields of cyclic hexa- and octameric products. X-ray crystallographic analysis revealed that the octamer adopts a C_4 -symmetrical conformation in the solid state and stacks to form hollow tubular structures with internal diameters around 1 nm (Figure 13).^[126] Following a similar procedure, achiral oligomers of D- and L-rhamnopyranose (RP) as well as D- and L-mannopyranose (MP) were prepared and characterized.^[127] The resulting cyclic hexasaccharide (from MP), octasaccharide (from RP), and decasaccharide (from RP) gave X-ray diffraction quality crystals. The structures of the octa-

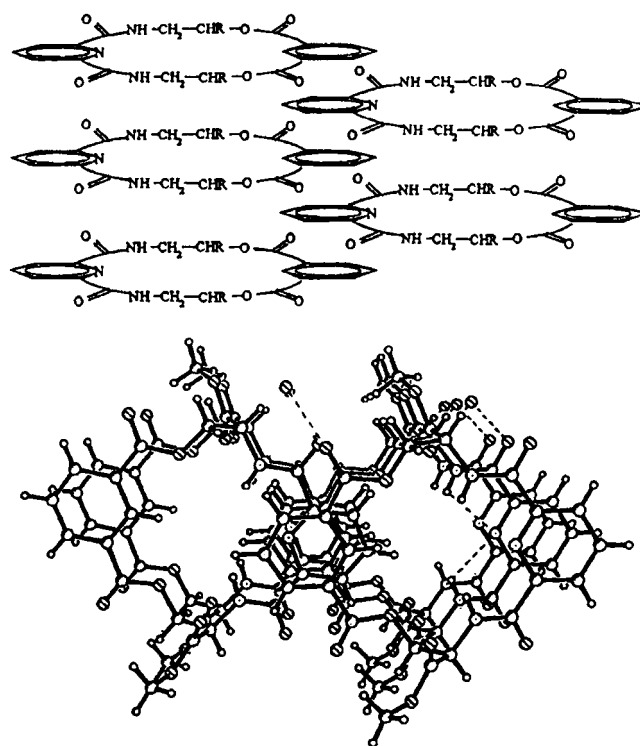


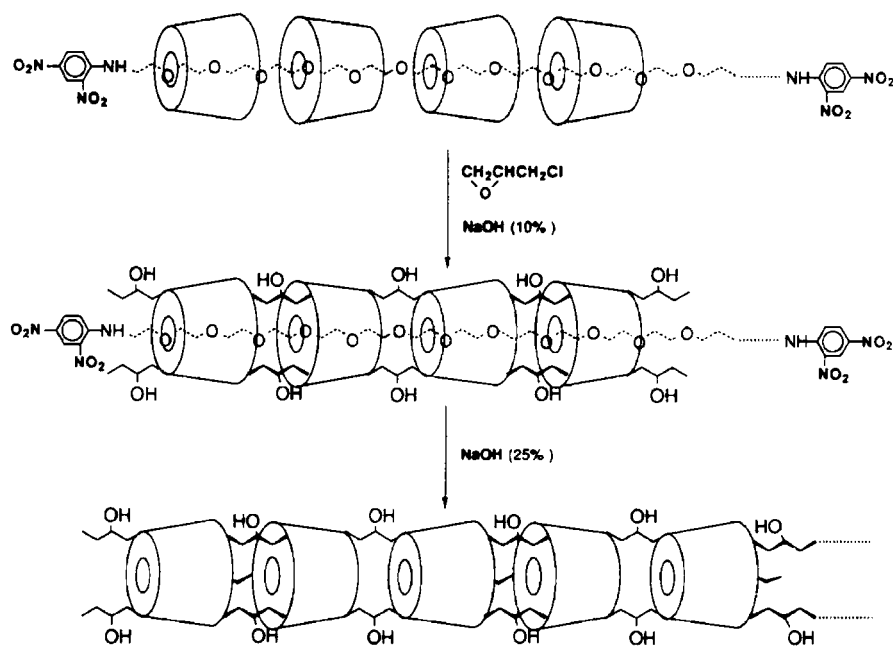
Figure 12. Top: A schematic depiction of the stacking interactions in the solid-state structure of a cyclic depsipeptide (serinophane). Note the alternate stacking of pyridyl and phenyl rings of adjacent serinophane columns. Bottom: The crystal structure of the same depsipeptide, which reveals the interdigitated aromatic rings and the 2.35 Å open channel through the assembly.^[110] Reprinted with permission from ref. [110]. Copyright (1998) American Chemical Society.

saccharide^[127] and the decasaccharide^[128] were tubular, while the hexasaccharide (from MP)^[128] formed a parquet-like superstructure. In all cases, included solvent molecules were observed within the macrocyclic cavities, which suggests the possibility of interesting host–guest properties for these structures.

4.6. Phenylacetylene Macrocycles

Zhang and Moore have examined the liquid crystalline behavior of shape-persistent phenylacetylene macrocycles (PAMs).^[129] Based on the previously documented propensity of PAMs with electron-withdrawing ester substituents to self-associate in solution,^[130, 131] similar long-chain alkyl analogues were initially examined. These compounds were found to be incapable of disordering into isotropic liquid crystals, presumably due to numerous favorable π -stacking interactions. However, differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analysis of isomeric acylated phenolic PAMs revealed both discotic nematic and columnar phases consistent with tubular ring stacking.^[129] Modeling indicated that the expected tubular structures possess an internal hydrogen to hydrogen distance of approximately 8 Å.

In related work, Moore and co-workers have studied the solid-state assembly of PAMs bearing hydrogen-bonding functionalities.^[132] X-ray crystallographic analysis revealed that the phenolic derivative forms two-dimensional hydrogen-



Scheme 4. Formation of a cyclodextrin nanotube by covalent capture of a polyrotaxane precursor. Treatment of the noncovalent assembly with epichlorohydrin captures the cyclodextrins to yield a molecular tube that is unoccluded after removal of the poly(ethylene glycol) thread.^[120] Reprinted with permission from *Nature* **1993**, 364, 516–518. Copyright (1993) Macmillan Magazines Ltd.

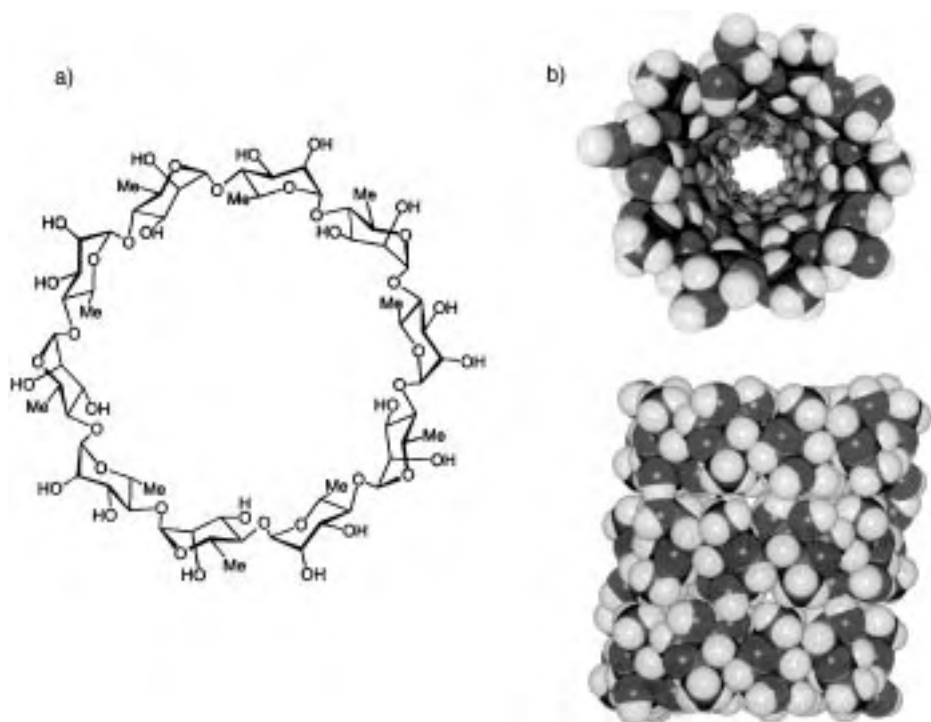


Figure 13. a) Chemical structure of cyclic D,L-rhamnopranose, which forms a solid-state tubular structure. b) Views along the cylindrical axis (top) and perpendicular to the cylindrical axis (bottom).^[126]

bonding networks which stack so as to maintain registry between the macrocyclic cavities (Figure 14). The resulting extended channel structures are filled with solvent molecules. In principle, properties such as pore size and solvophilicity can be varied by covalent modification of PAM precursors.

4.7. Tubular Mesophases from Macrocyclic Precursors

In 1985 a report from Lehn and co-workers described the first attempts at preparing liquid crystals exhibiting columnar phases consisting of stacked macrocyclic molecules.^[133] A number of cyclic hexaamines bearing long-chain *N*-alkyl substituents were synthesized. Results from XRD analyses of the resulting mesophases proved consistent with the expected columnar mesomorphic order. A model was proposed involving supramolecular arrangement of the macrocyclic mesogens into parallel, hollow columns. Later XRD analysis of brominated analogues confirmed the anticipated hexagonal columnar mesomorphism, which strongly supports the proposed tubular structures.^[134]

5. Sector-Assembly Motifs

The previous sections have detailed ways in which macrocycles and coiled molecules can self-organize into tubular materials by virtue of their well-defined shape. In those examples, cylindrical shape is immediately apparent from the monomeric species; pore size is defined by the degree of coiling or the ring size. A more complex approach to tubular constructs relies on the non-covalent assembly of wedge- or sector-shaped subunits to create molecular curvature. Conceptually, such an approach is similar to the stacking of molecular discs; however, this strategy demands higher order self-assembly as the discs are now separated into many sectors. This assembly topology^[135] has been visually demonstrated in Whitesides and co-workers' exploration of mesoscale assembly^[135] as well as in his earlier studies on the construction of molecular "rosettes", formed from the molecular recognition of melamine with cyanuric acid.^[135–138] Notably, the bismelamine–bisocyanuric acid variant of this self-assembly system forms "nanorods" through polymerization mediated by hydrogen bonds, although it is unclear whether or not an internal pore is formed upon polymerization.^[139]

Interestingly, this elaborate sector approach to tubular materials can be executed using perhaps the simplest possible starting materials as molecular sectors: lipids. Lipids are

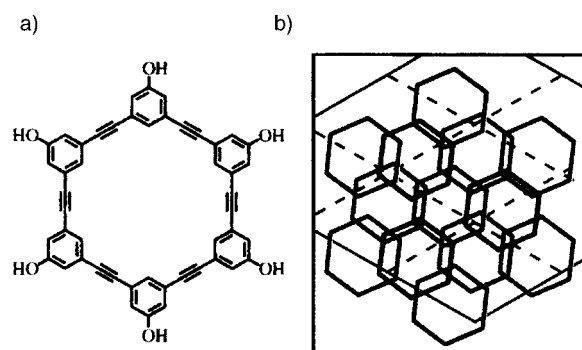


Figure 14. a) Chemical structure of the nanotube-forming phenolic acetylene macrocycle. b) Schematic representation of the crystal packing in the crystal structure. The macrocycles form a two-dimensional hexagonal closest packing which is reinforced by hydrogen bonding between phenolic substituents on adjacent macrocycles.^[132] Reprinted with permission from *Nature* **1994**, 371, 591–593. Copyright (1994) Macmillan Magazines Ltd.

among the most common biological amphiphiles, typically composed of long hydrocarbon chains coupled to a polar headgroup. Variations within this basic framework alter the lipid molecular shape, which allows lipid assemblies to access a wide range of structural morphologies, from micellar and hexagonal (H_{II}) phases to the lamellar (L_a) structure found in biomembranes (Table 1).^[140–142] The formation of these different structures in aqueous media is driven by exclusion of water, which provides the aggregate in which hydrocarbon chains are most efficiently close-packed against one another while the polar headgroups remain exposed to the solvent. Cylindrical structures have been formed from lipids that assemble in both lamellar and nonlamellar topologies. Although a detailed understanding of lipid aggregate topology requires quantitative thermodynamic consideration,^[140–143] a qualitative rationalization of aggregate morphology can be derived from evaluation of the molecular dimensions of the

individual lipid (Table 1). Lipid molecular shape can be generally described by three parameters: S_0 is the area of the polar headgroup, l is the maximum molecular length, and v is the molecular volume of the hydrophobic domain.^[144] The quotient v/IS_0 is called the *critical packing parameter*; essentially, it is the ratio of the interfacial area of the hydrophobic and hydrophilic regions. If $\frac{1}{2} \leq v/IS_0 \leq 1$, then the lipid is approximately cylindrical and a low-curvature aggregation topology such as the L_a bilayer phase provides optimum burial of the hydrophobic surface area and is therefore favored to form. Similarly, if $v/IS_0 \leq \frac{1}{3}$, then the polar head of the amphiphilic molecule is larger than its nonpolar domain, the molecular shape is inverse conical, and the formation of micellar-type aggregates with the polar headgroups exposed and the nonpolar regions packed against one another will be favored. Conversely, if $v/IS_0 > 1$, then the nonpolar region of the amphiphile is larger than the polar domain, the molecular shape is the cone, and a hexagonal (H_{II}) phase can be formed. Thus, lipid choice allows a measure of control over the consequent aggregate morphology.

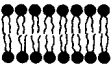
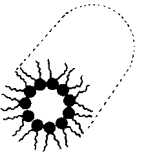
5.1. Assembly of Disc Sectors: Hexagonal Lipid Phases

The earliest reported examples of tubular lipid assemblies are represented by lipids in the inverse hexagonal phase. Lipids with a high spontaneous curvature (that is, a “wedge” shape) are especially likely to form these tubular phases, in which ordered polar headgroups line water-filled columns that are insulated from one another by disordered hydrophobic lipid tails (Table 1). Like many lipid phases, the formation of this phase is highly dependent on lipid shape and conditions, such as temperature, pressure, concentration, and extent of hydration,^[145, 146] which can strongly influence the diameter of these water-filled channels. Researchers have sought to capture these self-assembled porous materials by phase polymerization with varied methods.^[147] O’Brien and co-workers have worked extensively with modified lipids which bear the naturally occurring phosphoethanolamine headgroup and dienoyl functionality in the lipid tail;^[148] the small phosphoethanolamine head group and unsaturated acyl chains dictate hexagonal phase formation while the dienes allow for phase polymerization by addition of redox initiators at elevated temperatures.

5.2. Inverse Hexagonal Phases from Artificial Amphiphiles

The general concepts revealed from the study of structure–phase relationships displayed by natural lipids can be readily applied to artificial systems in which a specific three-dimensional order is desired. Percec and co-workers have pioneered studies on the behavior of amphiphiles based on a gallate core (Figure 15) in which the three phenoxy groups are alkylated with hydrophobic functionalities while the 1-carboxyl group is rendered hydrophilic through esterification or ionization, to yield a wedge-shaped molecule that readily forms a hexagonal columnar liquid-crystalline phase (see refs. [149–152] and

Table 1. Molecular shapes and critical packing parameters v/IS_0 for some lipids are shown, as well as the expected phase morphology that arises from particular shapes.^[142] Reprinted with permission from ref. [142]. Copyright (1989) Springer New York.

Lipid	Phase	Molecular shape	v/IS_0
lysophospholipids detergents	 micellar	 inverted cone	$< \frac{1}{3}$ (sphere)
phosphatidylcholine sphingomyelin phosphatidylserine phosphatidylinositol phosphatidic acid cardiolipin digalactosyldiglyceride	 bilayer	 cylinder	$\frac{1}{3}$ to $\frac{1}{2}$ (globular shapes; rods)
phosphatidylethanolamine (unsaturated) cardiolipin – Ca^{2+} phosphatidic acid – Ca^{2+} (pH < 6.0) phosphatidic acid (pH < 3.0) monogalactosyldiglyceride	 hexagonal (H_{II})	 cone	> 1

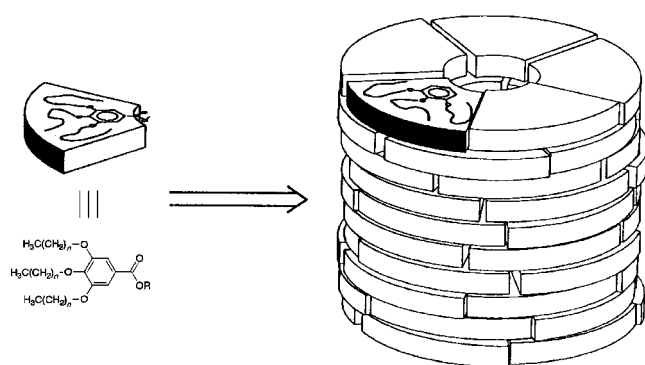
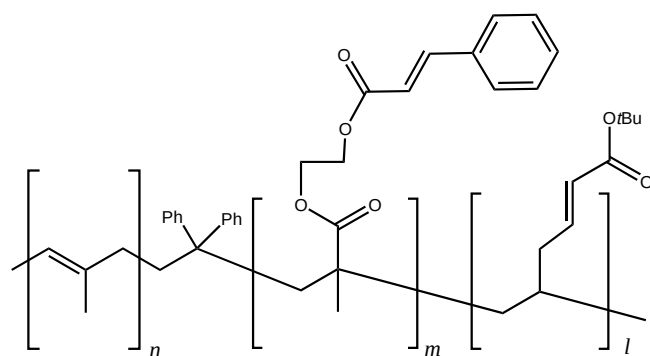


Figure 15. Schematic depiction of the assembly of a hexagonal phase from a synthetic amphiphile derived from gallic acid. The sector shape of the trialkylated gallate results in the formation of columnar liquid-crystalline arrays.^[149]

references therein). These molecules apparently assemble in a discotic fashion with the hydrophilic benzoate groups pointing towards one another in the center of the “disc”. Indeed, when the gallic acid nucleus is esterified with oligoethylene glycols the hexagonal phase is stabilized by the addition of lithium and sodium salts, as judged by increased phase transition temperatures from the hexagonal phase to the isotropic phase (melting).^[153] This suggests that the metals cooperatively bind to multiple gallate derivatives in the center of the self-assembled column, though they may also stabilize the assembly by enhancing hydrophobic interactions.

5.3. Nanotubes from Block Copolymers

Recent work from Stewart and Liu demonstrates another approach towards tubular nanostructures. By using a triblock copolymer of the type shown in Scheme 5 composed of



Scheme 5. Chemical structure of a triblock copolymer, in which the ratio of isoprene, cinnamoyl ethyl methacrylate, and *tert*-butyl acrylate is approximately 1:1:6; $n = 130$, $m = 130$, $l = 800$.^[154]

polyisoprene, poly(2-cinnamoyl ethyl methacrylate), and poly(*tert*-butyl acrylate) blocks in an approximate 1:1:6 ratio, they formed cylindrical micelles with an isoprene core. The assembly was then cross-linked with UV light to provide a stable covalent structure. The polyisoprene core, unreactive with UV light, was then decomposed by ozonolysis to yield a hollow tube of cross-linked acrylate polymer.^[154] The cylin-

drical micelles appear to be approximately 65 nm in diameter, as observed by transmission electron microscopy (TEM) when the micelles were stained with RuO_4 . Compelling evidence for tube formation is afforded by increased electron transmission in the center of the polymer strands after ozonolysis; a light-colored stripe is seen running down the middle of each strand, suggestive of a hollow interior (Figure 16). Interestingly, the authors were apparently able to fill the tubes by treatment with rhodamine B dye, which restores the TEM absorbance levels to those prior to ozonolysis.

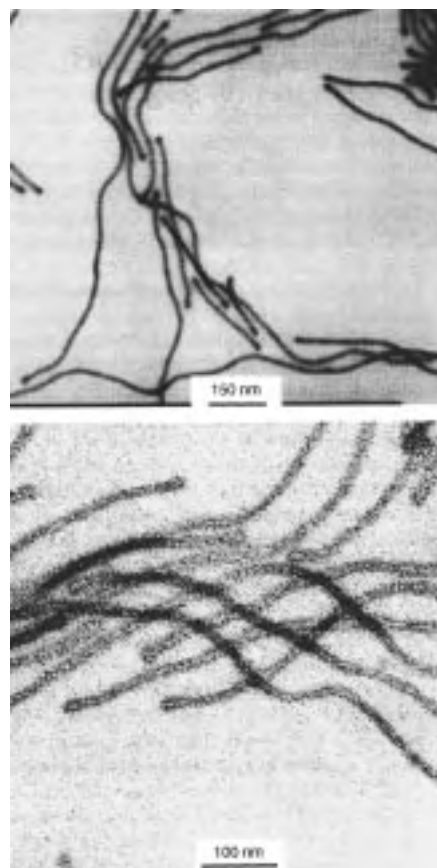


Figure 16. TEM images of cylindrical micelles of the triblock polymer from Scheme 5), before (top) and after (bottom) ozonolysis of the isoprene core. The micelles (top) were stained with OsO_4 and the ozonolysed product with RuO_4 . The lighter core of the ozonolysed micelle suggests the formation of polymeric tubes.^[154]

6. Folded-Sheet Motif

Lipid tubules composed of bilayer sheets curled into cylinders have been observed in various surfactant systems, derived from amino acids,^[155–157] galactocerebrosides,^[158] and other unnatural lipids. Particular attention has been given to the tubular lipid assemblies formed from the synthetic lipid 1,2-bis(tricos-10-12-diynoyl)-*sn*-glycerol-3-phosphocholine, which bears a zwitterionic headgroup and diacetylenic unsaturation in each hydrocarbon chain. Yager and Schoen first reported in 1984 that a suspension of this lipid in alcohol–water mixtures results in the spontaneous formation of tubular structures upon cooling below the lipid melting

temperature.^[159, 160] These cylindrical aggregates were found to be composed of curved bilayer sheets in which the lipid chain axis is perpendicular to the cylinder axis (Figure 17). Moreover, these constructs were hollow and open-ended with

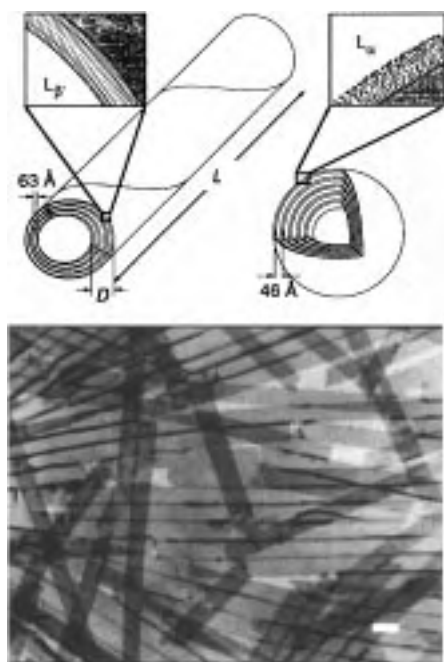


Figure 17. Top: Schematic depiction of the differences in lipid packing of lipids with diacetylenic groups in the hydrophobic section and natural fluid-phase lipids (D = thickness, L = length of the tube). The first case results in tubule formation and the second in spherical liposome formation. The rigid shape of the diacetylenic lipids induces a bilayer curvature which leads to tubule formation, whereas the fluid natural lipids are much more disordered, resulting in a more symmetric spherical lipid morphology. Bottom: Negatively stained electron micrographs of single bilayer 1,2-bis(tricosyl-10,12-diinoyl)-*sn*-glycero-3-phosphocholine tubules in methanol/water.^[167] Tubule diameter is approximately $0.75\ \mu\text{m}$.

a typical diameter of $0.5\ \mu\text{m}$ and lengths ranging from $50\text{--}200\ \mu\text{m}$. Varying self-assembly conditions such as temperature, lipid concentration, and solvent can control lipid tubule size. When methanol is used as the aqueous cosolvent at low lipid concentrations, unilamellar (single-walled) tubules are formed,^[161] whereas an ethanol/water lipid suspension consists of largely multilamellar tubules, with $5\text{--}10$ bilayers per tubule wall.^[162] Additionally, spherical multilamellar vesicles (MLVs) and cylindrical MLVs (tubules) are found on the same thermal landscape with the spherical liposomes occupying the higher temperature regime; thus heating and cooling lipid suspensions allow for reversible cycling between the two morphologies.^[160] Interestingly, the length of tubules formed is closely linked to the cooling rate of lipid suspensions from the spherical MLV regime, and therefore it is possible to control both tubule wall thickness and tubule length to some degree.^[163]

The origin of tubule formation is not entirely understood, though the bilayer curvature required for cylinder formation is probably a result of unique packing requirements caused by the diacetylene functionality in the lipid acyl chains. This surface curvature apparently induces a preferential lipid

orientation that has the ultimate consequence of twisting the bilayer to form an optically active lipid aggregate.^[164, 165] Indeed, the tubules exhibit a significant Cotton effect when analyzed by CD spectroscopy,^[166, 167] whereas the spherical MLVs do not provide a detectable dichroic signal. Furthermore, freeze–fracture electron microscopy revealed a right-handed helical twist in each tubule, demonstrating the chiroselective nature of assembly.^[160]

While much effort has been devoted to the stabilization of these lipid assemblies since first reported by Yager and Schoen in 1984, diyne polymerization-phase capture does not appear to be a viable strategy as the enyne polymeric product has considerably different conformational requirements than the curved bilayer. There have been accounts of successful capture of the tubule shape through use of the lipid assembly as a template for the deposition of more rugged materials, such as nickel, copper, or magnetic alloys.^[168]

7. Potential Applications

7.1. β -Helical Biosensors

Gramicidin A has been exploited in a novel biosensor apparatus that capitalizes on the dimeric state of the active β -helix channel.^[169] In this system, biomolecule recognition (that is, antibody–antigen binding) is coupled to either an increase or decrease in the number of active channel species in a solid-supported lipid bilayer (Figure 18). A gramicidin peptide is

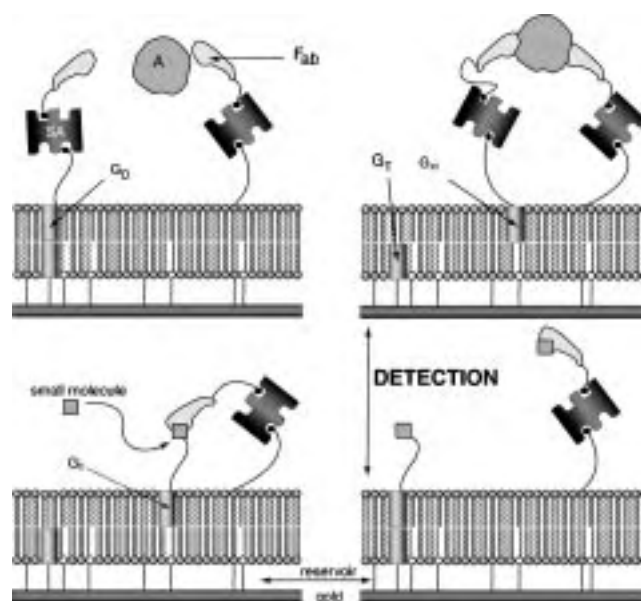


Figure 18. Schematic representation of an ion-channel switch biosensor.^[169] A lipid bilayer is tethered onto a gold surface by sulfur–gold bonds between the thiol-terminated membrane-spanning lipids and the surface. Gramicidin molecules are similarly surface tethered (G_T) and stochastically interact with free gramicidins (G_a or G_b) that diffuse into the upper bilayer; this forms conducting gramicidin dimers (G_D). The conducting dimers report the binding of a small molecule to a membrane-bound receptor (antibody fragment F_{ab}) by an increase in conductance (bottom, left to right). The disruption of the dimer, and therefore a drop in conductance, (top, left to right) reports the binding of antigen A by cross-linking the membrane-bound receptor and a gramicidin-bound receptor.

covalently bound to the gold support through a linker thiol–gold bond, as are some fully membrane-spanning lipids, which serve to stabilize the bilayer. Another gramicidin peptide is also incorporated into the membrane, and is not bound to the support, but is instead functionalized with a biomolecular recognition element, such as an antibody or antigen. This second peptide diffuses freely in the top monolayer, occasionally recognizing the lower monolayer gramicidin peptide and opening a channel, which can be detected by electrical conductance measurements. An identical antibody or antigen is similarly attached to a support-anchored lipid, and thus when a bivalent analyte (molecule A) binds, the diffusing gramicidin peptide is bound, the channel is broken, and conductance stops (Figure 18, top). When a competing analyte is added to the medium, the gramicidin is freed, the channel restored, and the conductance resumes (Figure 18, bottom), thereby allowing the detection of small molecule analytes.

In preliminary studies aimed at preparing ion selective membranes, Roemer, Lorenzi, and Weisenhorn have examined thin films of the synthetic $\beta^{4,4}$ -helical oligopeptide Boc-D-Val-(L-Val-D-Val)₇-OMe. These authors found that, at low surface pressures, Langmuir films of the peptide lie flat at the air–water interface, while at higher pressures the peptide reorients itself with its helical axis perpendicular to the surface of the water.^[170] Atomic force microscopy (AFM), ellipsometry, and grazing angle IR measurements of Langmuir–Blodgett films supported on ultraflat silicon surfaces corroborated these conclusions.^[171]

7.2. Biosensors from Cyclic D,L-Peptides

As an approach toward the design of diffusion-limited sensors, cyclic eight-residue D,L- α -peptides have been assembled into oriented tubular structures and supported in organosulfur self-assembled monolayers (SAM) on gold films (Figure 19).^[172, 173] The structural properties of SAM-supported peptide nanotubes have been analyzed by grazing-angle

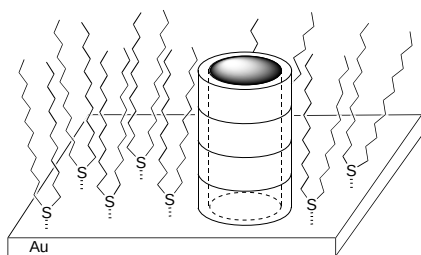


Figure 19. Schematic depiction of a biosensor similar to that in Figure 18 which is based on cyclic D,L-peptides. A gold surface enjoys protection by a monolayer of thioethers that is punctuated by cyclic peptide stacks. These stacks would then allow the size-selective sensing of ions in solution.^[173]

FT-IR and their functional properties by cyclic voltammetry and impedance spectroscopy. These studies have demonstrated the feasibility of diffusion-limited size-selective ion sensing based on supported tubular biomaterials.

7.2.1. Small-Molecule Detection with Cyclic D,L-Peptide Adapters

Recent work from the Bayley laboratory has demonstrated the utility of a natural pore-forming protein as a molecular biosensor. Bayley and co-workers have coupled small-molecule (or ion) binding events to the flow of electrical current through a single molecular channel in a membrane. Thus, a molecular recognition event can be dramatically amplified above background electrical noise and be detected with exquisite sensitivity. Previously, genetic engineering of the heptameric toxin α -haemolysin to incorporate metal-binding ligands into the lumen of the molecular channel allowed the quantitative detection of various divalent metal ions in solution.^[174] However, small-molecule detection using the haemolysin channel proved to be a less tractable problem as it was not clear how to design a substrate binding pocket into the lumen structure. To address this, a cyclodextrin molecule was used as a “molecular adapter”, which fits snugly within the cylindrical lumen of haemolysin, coaxial with the protein pore (Figure 20). Thus, all molecules flowing through the haemolysin channel were filtered through the cyclodextrin molecular adapter.^[175] This allowed researchers to detect the small molecules that bound to cyclodextrin and blocked ion flow, which was registered as a decrease of channel conductance (Figure 21).

In an effort to find molecular adapters that are more readily tailored to detect a broader range of substrates, cyclic D,L-octapeptides were studied for their ability to noncovalently modify haemolysin and detect small-molecule substrates. These cyclic peptide adapters possess a clear advantage over the cyclodextrins in that the functionality presented at the pore aperture is easily altered by changing the amino acid sequence. In this fashion, the sensor selectivity can be manipulated by choice of peptide adapter, rather than the decidedly more involved process of engineering the protein pore itself. Furthermore, the facility of cyclic peptide synthesis renders chemical libraries of peptides accessible so that adapters for a wide range of substrates may be readily found. This approach takes advantage of the relatively sequence-independent flat-disc shape of cyclic D,L-peptides; not only does this rigid shape predispose the peptides towards self-assembly, but it provides a reliable platform for the presentation of chemical functionality (Figure 20d). A recent examination of this peptide-modified ion-channel biosensor system has shown that various polyanionic small organic molecules (Figure 20e) can be detected, including the second messenger inositol triphosphate (IP₃).^[176] Clearly, this biosensor system demonstrates how tubular shape can be flexibly controlled in order to maximize chemical selectivity.

7.3. Antibiotic Properties/Targeted Cytotoxicity

We note that self-assembling cyclic D,L-peptide nanotubes exhibit significant *in vitro* antibacterial activities and may therefore serve as lead compounds in the development of new antimicrobial and cytotoxic agents.^[177] Attachment of bulky groups to the cyclic peptide side chains has been shown to

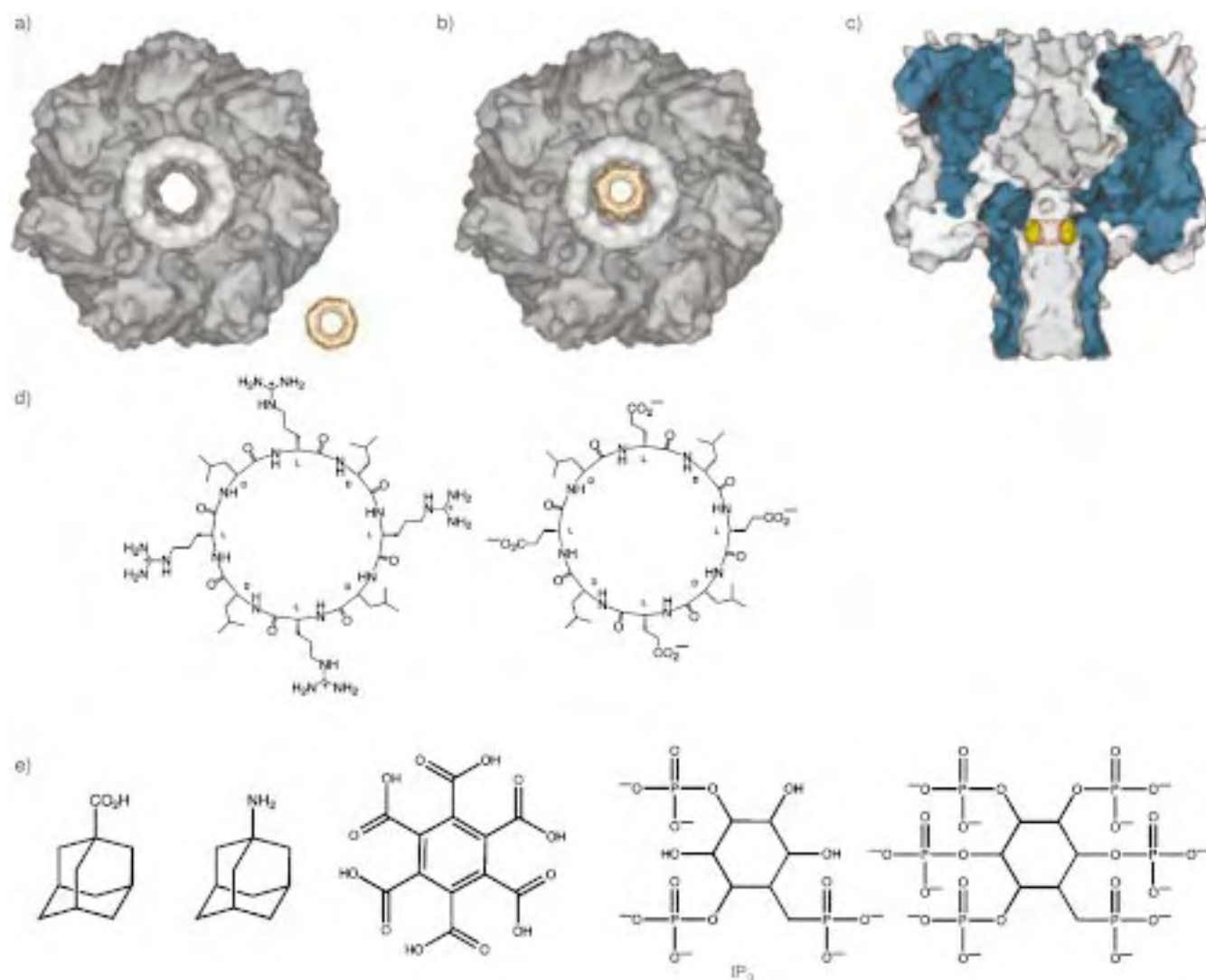


Figure 20. a)–c) Molecular graphics representations of the interaction between α -haemolysin (HL) and β -cyclodextrin as a molecular adapter. a) View along the pore axis without adapter. b) View along the pore axis with an inserted adapter. c) View of a sagittal section of the heptameric HL pore, with the adapter in place, where it is expected to be lodged at a site of constriction of the pore.^[175] d) Chemical structures of the cyclic D,L-peptide molecular adapters used to detect small polyanionic molecules (e). Reprinted with permission from *Nature* **1999**, 398, 686–690. Copyright (1999) Macmillan Magazines Ltd.

sterically inhibit ring stacking and therefore channel formation, suggesting the possibility of derivatizing the cyclic peptide subunits with a specific cell-targeting motif through an enzymatically labile bond. Cleavage of the targeting group at the specific cell-recognition site would create a high concentration of active peptides, thereby favoring channel formation and leading to disruption of transmembrane gradients. Furthermore, the nonnatural alternating D,L-configuration may increase the bioavailability of these peptides by enhancing their resistance to proteolytic degradation.

7.4. Electronic Properties

Recently, several computational studies employing density functional methods have focused on elucidating the electronic properties of cyclic-D,L-octapeptide nanotubes. The results of Takeda and co-workers suggest that intersubunit hydrogen bonding may delocalize electrons and holes toward the tube

axis, so that band conduction might occur through the interring hydrogen bonds.^[178] More recently, Takeda and co-workers have examined the role of intra- and inter-ring hydrogen bonds in determining the electronic structure of peptide nanotubes and found that the electronic band-edge states are strongly dependent on the inter-ring hydrogen bonds.^[179] Employing calculations with gradient-corrected exchange-correlation potentials, Carloni et al. have predicted a large gap in the low-energy electronic excitation spectrum, with both extended and localized states near the gap.^[180] These findings are supported by the results of Lewis et al., which indicate a HOMO–LUMO gap of approximately 5 eV for the nanotube structure, consistent with a transparent material and suggesting interesting bioelectronic device applications for the cyclic peptide nanotube systems.^[181] Jishi et al. have calculated a 4.62 eV HOMO–LUMO gap and found that the nanotubes are insulators that could function as inert vessels in which foreign guest atoms may be incorporated.^[182]

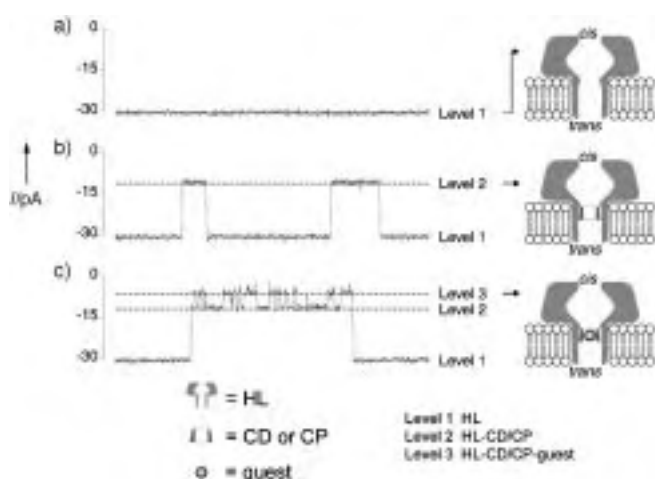


Figure 21. Conductance measurements for a bilayer, which demonstrate the utility of α -hemolysin with a molecular adapter as a small-molecule biosensor. Level 1 indicates the conductance across a membrane modified with only α -hemolysin (HL), level 2 indicates the decreased conductance level caused by binding of a molecular adapter within the HL lumen, and level 3 indicates the further reduction in conductance caused by stochastic binding of guests to the molecular adapter while it is bound inside the HL channel. The data shown correspond to experiments using β -cyclodextrin as an adapter^[175] and adamantamine hydrochloride as a guest; similar results have been found using cyclic D,L-peptides (CP; Figure 20d) as adapters. Reprinted with permission from *Nature* **1999**, 398, 686–690. Copyright (1999) Macmillan Magazines Ltd.

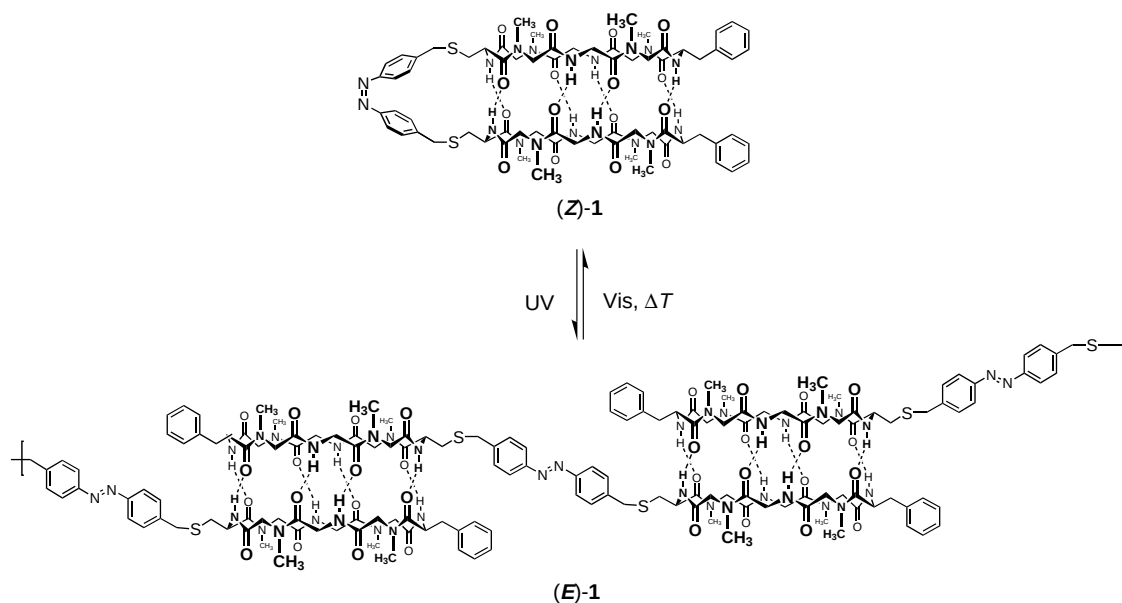
7.5. Photoresponsive Materials

Much research has been devoted to the study of molecules whose physical properties can be reversibly switched using light.^[183–189] Such systems are expected to be of great utility in the synthesis of read-write-erase optical data storage devices, as well as in “smart polymers”.^[190] For these applications, two significantly different and stable molecular states that are bridged by distinct light inputs are required. This would provide a state-switchable system in which the signal-to-noise

ratio (that is, the difference between states 1 and 2) is maximized. Thus, efforts have been made to couple secondary protein-folding with light-induced transitions, as the cooperative folding process is an all-or-none phenomenon that separates two very distinct states: compact, folded peptide and random-coil, unfolded peptide.^[191] Nucleation of certain peptide motifs such as a turn of an α -helix is known to rapidly induce the folding process.^[192, 193] Thus, if critical turn conformations could be reversibly controlled by light, one would then arrive at an efficient photo-switchable peptide system that could be radiatively folded and unfolded and possibly employed in the aforementioned applications.

Recent work in our lab has been directed towards such photoswitchable systems. Building upon studies of covalently captured cyclic D,L-peptides, we have examined a covalent dimeric system in which the two cyclic peptides are connected through an azobenzene spacer (Scheme 6).^[194] The peptides were further modified by *N*-methylation of alternate amides, restricting the hydrogen-bonding capability to one face of each flat-ring peptide. Modeling indicated that only the *Z* conformation of the azobenzene would permit intramolecular hydrogen bonding between the two linked peptides, to form a cylindrical dimer, whereas the *E* conformation would prevent close intramolecular interactions and would result in the formation of noncovalent hydrogen-bonded oligomers of azo-linked peptides. The *E* $\rightarrow$ *Z* and *Z* $\rightarrow$ *E* isomerizations were induced by irradiation at 366 nm and visible light, respectively. Conversion between *Z* and *E* yields an 85:15 ratio at the photostationary state. As expected, intramolecular hydrogen bonding enhanced the stability of the *Z* form, resulting in a rare quantitative *E* $\rightarrow$ *Z* transition. Furthermore, kinetic experiments revealed that the thermal isomerization in the dark from *Z* $\rightarrow$ *E* was 7.5 times slower in the peptide system than with 4,4'-dimethylazobenzene.

Although this system proved to be highly reversible in solution, it was unclear whether or not there would be enough



Scheme 6. Schematic illustration of the azo-linked cyclic D,L-peptide dimer and its light- and heat-mediated equilibria between the monomeric *cis* isomer and the oligomeric hydrogen-bonded *trans* isomer.^[194]

free volume to allow isomerization in the solid state. Thus, we further examined the behavior of these linked dimers in two-dimensional solids, or Langmuir thin films.^[195] Both isomers readily formed stable films, which were more robust than those produced with monomeric, nonalkylated cyclic peptides.^[196] Indeed, similar photoisomerization reversibility was found in thin films. However, though both *E* and *Z* isomers have a similar area/molecule, scanning force microscopy revealed that the *E* isomer is predisposed to form molecular bilayers, whereas the *Z* isomer prefers to pack in a monolayer. Thus, significant differences in surface pressure arise upon isomerization; essentially, the system undergoes a reversible and substantial change in organization properties upon exposure to specific light wavelengths. Further development in this promising system may therefore lead to smart materials that could change their macroscopic properties in response to light.

7.6. Biomaterials

Our laboratory has also investigated the formation and stabilization of transition metal nanoclusters (quantum dots) on the surface of cyclic D,L-peptide nanotubes.^[197] These studies were inspired by natural biomineralization processes which are thought to require the display of oriented functionalities on protein and oligosaccharide templates. Indeed, similar work has been done using the functionalized surfaces of lipid tubules to template crystallization of minerals.^[198] In preliminary studies the organized array of carboxylic acid groups on the crystalline surface of a peptide nanotube was used to nucleate the room temperature deposition of nearly monodispersed (approximately 3 nm large) copper(I) oxide nanoclusters (Figure 22). The resulting nanocomposite material was characterized by high-resolution TEM and electron energy loss spectroscopy (EELS). The regular presentation of functionality of the tube surface may also provide a useful substrate for the crystallization of minerals.

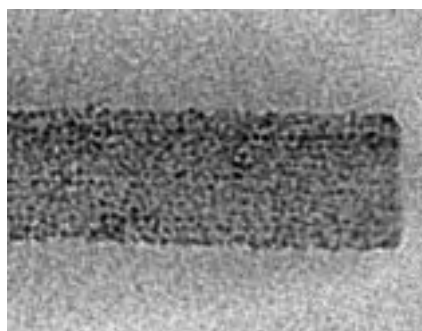
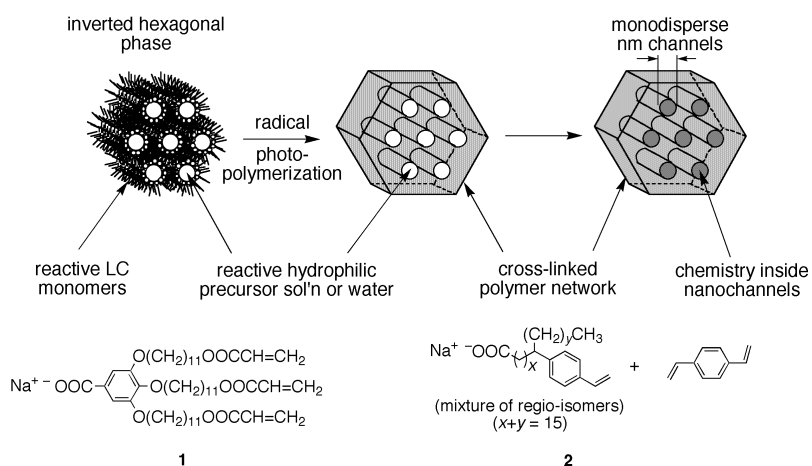


Figure 22. High resolution cryo-TEM of a copper oxide nanocomposite deposited on a *cyclo*[-Gln-D-Ala-Gln-D-Ala]₂- self-assembled microcrystal. The copper(I) clusters have an average radius of 1.5 nm.^[197]

7.7. Ordered Nanocomposites

Although Percec has demonstrated the ability of metal substrates to bind to the decorated columnar interior of hexagonal phases from gallate-based mesogens (see Section 5.2), the tubular core of this hexagonal phase was first fully exploited by Gin and co-workers, who prepared defined polymer–polymer nanocomposites of a gallate-based hexagonal phase and poly(*p*-phenylenevinylene) (PPV) in which the PPV threaded the channel at the center of the gallate column.^[199] Gin and co-workers' modifications of the gallate platform incorporated acrylate functionality at the end of the phenoxy hydrophobic tails as well as the sodium salt of gallic acid, to allow formation of the hexagonal phase as an aqueous suspension (Compound **1**, Scheme 7). When this mesogen was

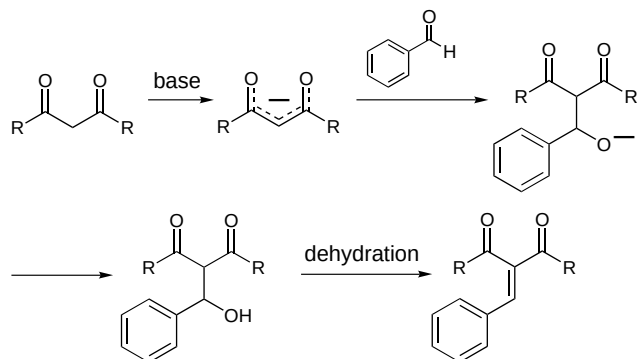


Scheme 7. Synthetic approach to nanocomposite materials using polymerizable inverse hexagonal liquid-crystalline phases. Compounds **1** and **2** are known to form inverted hexagonal phases that can be photocross-linked (with or without divinyl benzene) to capture the columnar arrangement of amphiphiles with water-soluble substrates trapped inside the nanometer scale channels.^[199, 205]

mixed with a water-soluble PPV precursor, the PPV precursor occupied the aqueous channel lined by the benzoate functionalities. Subsequent photoinitiated polymerization of the acrylate groups allowed for covalent phase capture of the nanocomposite while thermal treatment yielded the mesogen-insulated PPV material. The resulting PPV fluorescence is enhanced approximately four times over pure PPV, which indicates potent protection from self-quenching mechanisms^[200, 201] by the chain-dilution effect of the nonfluorescent matrix, although there may be other factors involved. The authors have also demonstrated the effective encapsulation of transition metal and lanthanide ions to introduce new properties into these nanocomposites. Composites with europium ions enhanced Eu^{III} luminescence due to the small degree of hydration of the composite core, although self-quenching through diffusion along the cylindrical axis is still possible. (For organic systems designed to site isolate Eu^{III} for the purposes of luminescence enhancement, see refs. [202, 203].) Thus, this method uses the cylindrical nature of the hexagonal phase to synthesize nanostructured materials in a fashion that appears quite general for preparing columnar arrays of water-soluble substrates.^[199, 204]

7.8. Chemical Catalysis

Gin and co-workers have further utilized the polymerization phase-capture strategy to obtain tubular materials that can catalyze the Knoevenagel condensation of ethyl cyanoacetate with benzaldehyde (Scheme 8).^[205] This catalytic power



Scheme 8. Hann–Lapworth mechanism of the Knoevenagel condensation.

is direct result of the cylindrical assembly. Using a carboxylate amphiphile (Compound **2**, Scheme 7) they have been able to form cylindrical micelle assemblies in which the water-filled pores of 10–15 Å diameter are lined with carboxylate groups. Addition of divinylbenzene and subsequent photocross-linking results in polymerization phase-capture of this tubular array. The enforced proximity of the carboxylates causes strong electrostatic repulsion and drives a substantial increase in the pK_a value^[206–209] to 5 pK units above the value for the free carboxylate in water. This renders the carboxylates into effective weak bases, which are known to catalyze the Knoevenagel condensation.^[210] The influence of local environment on chemical reactivity has been thoroughly exploited by enzymes and has also been demonstrated in other regular micellar and monolayer systems.^[211–214] Gin and co-workers' incorporation of these concepts into open, porous, and covalent structures provides a reasonable platform for exploration of organic heterogeneous catalysis, or "organic zeolitic" catalysts.^[205]

7.9. Slow-Release Drug Delivery

Price and co-workers have examined the possibility of using diyne lipid bilayer tubules or the "folded-sheet" tubes discussed earlier as slow-release drug-delivery vehicles, since the aqueous channels can readily be filled with water-soluble molecules. The high aspect ratio of these tubes renders them less sensitive to damage from osmotic pressure as the molecules are released. This principle was first tested with tetracycline, which was found to be released slowly over several months.^[215] Price then applied tubule-controlled release to address the problem of marine bio-fouling. To do this, tubules were coated with copper and dried to form microcapillary tubes,^[216] mixed with an antifouling epoxy resin, then painted onto fibreglass rods, which were exposed

to marine conditions. In contrast to a heavily fouled control rod with only the epoxy resin mixed with paint, the tubule-treated rod remained clean after six months of exposure,^[23, 217] indicating that tubular materials may be very useful for controlled release applications.

8. Summary and Outlook

A number of approaches to organic nanotubes have been presented in recent years. Some, like the β -helical channels, may require the context of a hydrophobic matrix such as a lipid bilayer to be useful. Steric compression caused by the syndiotactic backbone of β -helices provides the impetus of cylinder formation, but helical pitch remains difficult to control. In contrast, the *meta*-substituted phenylacetylene oligomers are well suited for reliable helical-cylinder formation, as the turn angle is rigidly fixed, and only one helical pitch can provide sufficient solvophobic backbone burial. However, it seems that these linear systems are limited to low-oligomer tubular states, which may decrease their potential applications. In both these systems, large entropic gains are made upon cyclization, which result in readily-formed solid-state tubular arrays of stacked phenylacetylene macrocycles, oligosaccharides, and cyclic D,L-peptides. In the cyclic form, pore size becomes well-defined and controllable. Thus, design of function is greatly facilitated; one has a reliable repeat unit that can be exploited to place functionality in a supramolecular lattice with molecular precision. Possible applications for such nanotubular structures are many and range from preparation of novel cytotoxic and controlled-release drug-delivery agents to catalytic and materials science applications, such as biomineralization and site isolation of chromophores or other reactive groups. Stacked cyclic molecules must utilize specific modes of self-assembly to assemble—however, in the cited examples, relatively simple and robust scaffolds of molecular recognition have been employed with great success. In the more fluid lipid systems, even simpler and less-specific recognition motifs are employed. Hydrophobic collapse of amphiphiles can result in extremely complex tubular arrays that are liquid crystalline in nature, yet very stable. Again, the pore size of these arrays is difficult to predict and may depend on dispersion conditions. As our collective understanding of the factors affecting self-assembly of macromolecules and amphiphiles grows, it seems likely that much of the future work in tubular assemblies will focus on cyclic and "sector" approaches, or combinations thereof, to cylindrically organized, and increasingly functional materials.

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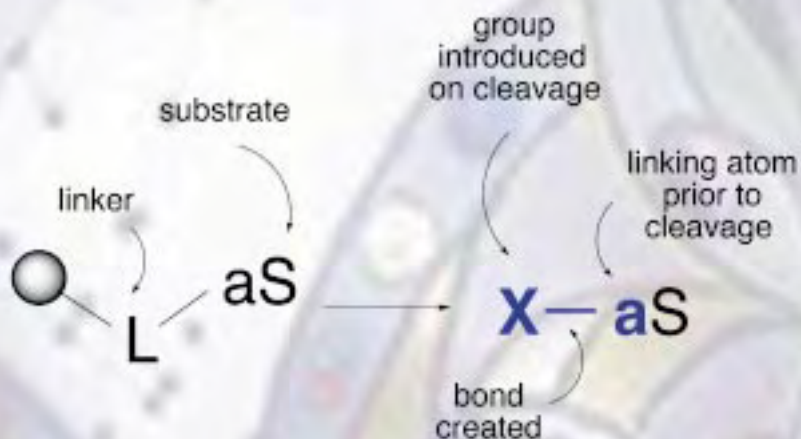
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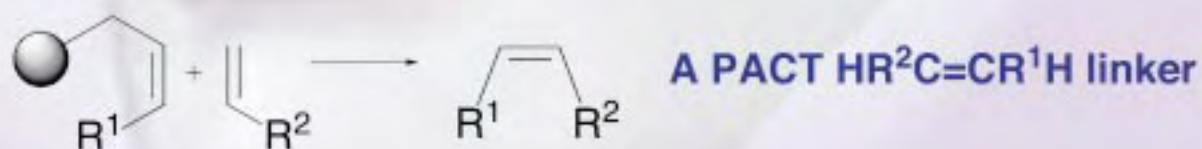
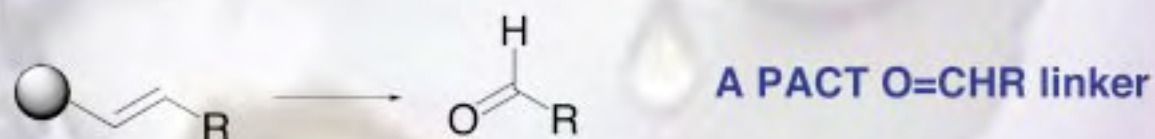
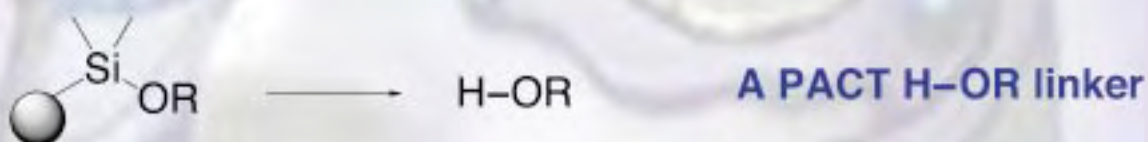
A Venetian Carnival in Solid-Phase Synthesis? Traceless Linkers Remain Incognito!

The Nomenclature Explained



The **P**oint of **A**ttachment of the substrate **S** is **C**onverted To **X-a**:

PACT **X-a**



Tracelessness Unmasked: A General Linker Nomenclature

Alex C. Comely* and Susan E. Gibson* (née Thomas)

Nowadays it is rare to find an issue of a major chemistry journal without at least one article on solid-phase synthesis. This is hardly surprising: the technique promises an end to arduous work-up procedures and the ability to facilitate the creation of vast libraries of compounds using combinatorial techniques. No longer is the technique only of interest to those involved in peptide synthesis: an enormous variety of product classes have now been prepared on and isolated from the solid phase. It is the “linker” which is the focus of this article. The linker’s

ultimate function is to release a product from the support into solution: it does this, without exception, with a chemical change to the product at the former linkage site. Some linkers, apparently, are “traceless”. But what, in fact, is “tracelessness”? Twenty years ago, in a climate where cleavage of a linker resulted in formation of a polar carboxylic acid as the vestige of the support, the concept was attractive. Today the chemist is faced with a myriad of novel linkers which have the ability to release products bearing most major functionalities at the for-

mer linkage site and we will argue here that the term “traceless”, although currently in widespread use, is meaningless. Instead, we propose a new categorization of linkers based on the functionality they release upon cleavage, and suggest a nomenclature to underpin this categorization. We anticipate that the article will also serve to highlight areas of linker technology in need of further research.

Keywords: combinatorial chemistry • solid-phase synthesis • traceless linkers

1. Introduction

The seeds of Merrifield’s pioneering solid-phase peptide synthesis have found fertile soil both in the academic world and the pharmaceutical industry.^[1] Indeed, the years since its invention have seen wide-ranging developments: for example, vast peptide libraries have been prepared and screened using the concept of combinatorial chemistry^[1a–h] and the “mix and split method”. These processes have been enormously facilitated by the advent of automation and progress in reaction monitoring. The preparation of other oligomers such as peptides, oligosaccharides, oligocarbamates, and peptide nucleic acids has been equally successful.

As drugs, however, peptides pose certain problems. Ready hydrolysis and low bioavailability limit their value, and the translation of a peptidic lead structure into a non-peptidic analogue is far from trivial. The chemical focus of research has hence diverged to accommodate the solid-phase synthesis of “small organic molecules” and therefore, inevitably,

the greater demands imposed by general organic chemistry.^[1i–o]

In terms of the chemistry performed on the polymer-bound substrate there can now be few reaction classes not at the chemist’s disposal and the excellent reviews compiled annually by researchers at Organon^[1p–r] are categorized with this in mind. Any solid-phase methodology, however, necessarily has one constraint: that the polymer–product adduct be unstable to a set of conditions which effect the product’s cleavage and isolation.

This constraint leads us to, perhaps, the most recent arena of research. The linker, the structural motif which temporarily joins the polymeric support and the substrate under manipulation, is of crucial importance.^[1s–z] Not only must it tolerate the conditions used to elaborate the substrate, it must cleave under conditions mild enough not to affect the product’s integrity. Unfortunately, such a proviso rules out a universal linker, namely, one suitable to every application, such that a catalogue of possible linkers is required containing one suitable for any synthetic sequence.

The linker clearly prescribes the revealed functionality at the former linkage site (the vestigial functionality) of the product as it is liberated. A legacy of solid-phase peptide synthesis is the release of carboxylic acids or amides from an ester- or amide-bound substrate. While entirely appropriate in peptide synthesis, this polar functionality is not always

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desirable in a more general arena. Efforts to address this problem have, in recent years, stimulated the evolution of so-called “traceless linkers”.

Traceless Linkers

A survey of the literature in this area will quickly betray a confusion, however. What, in fact, is “tracelessness”? The term refers to some quality of a liberated product, but opinion clearly differs and three quite distinct definitions are in current use. These can be illustrated using the classification of linker types depicted schematically in Figure 1. The first definition of a traceless linker (Type A), and that primarily cited by the chemical community, refers to the introduction of a hydrogen atom at the former linkage site, be this onto an alkyl- or aryl-bound scaffold. In the face of the ubiquity of this C–H “functionality” the definition is, perhaps, justified. However, slow and incremental deviation from this conceptual “ideal” leads us to the quagmire of what “tracelessness” is to most authors in the field. The conceptual “hydrogen” definition is now so dilated as to embrace the formation of alkenes, amines, heteroarenes, ethers, alcohols, aldehydes, ketones, and even the carboxylic acid derivatives that the new technologies originally intended to avoid. Perhaps in the sense that the former linkage site now bears no resemblance to the linker prior to cleavage it is “traceless”, but it is not easy to see how the term “traceless” remains meaningful or even valid.

A second definition of tracelessness has been attributed to linkers which belong to Type B in Figure 1, whereby cleavage results, usually from an aromatization or amine quaternization process, in what may be perceived as an overall reduction in the level of functionalization. For linkers that result in a chemical or connectivity change at the linkage site, this is arguably the strongest contender for the “traceless” title.

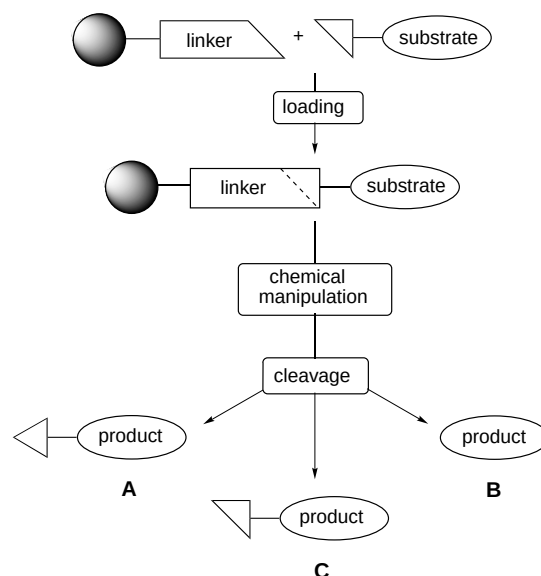


Figure 1. A schematic representation of the three linker types. Type A: Different functionality is incorporated on cleavage. Type B: The product has a reduced level of functionalization relative to the substrate prior to cleavage. Type C: The functionality released on cleavage is the same as the functionality loaded onto support.

Protecting group linkers, namely those which operate without overall chemical change at the linkage site, constitute a third category defined in the literature as “traceless”: these belong to Type C linkers in Figure 1 and are “traceless” in that the substrate linkage site before and after immobilization is identical.

“Tracelessness” has also been defined on occasions in terms of ubiquity: if, for example, cleavage creates an aromatic C–H bond on a monosubstituted arene product, the linker is

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“traceless” in the sense that the new C–H bond is indistinguishable from the four already present.

Confronted by such an amorphous definition, it is of no surprise that authors can so easily hoist the “traceless” flag over novel linker technologies. Nomenclature is essential to the efficient communication of ideas and a more rigid and comprehensible terminology will clear the mists from a rather cloudy aspect of this very important field.

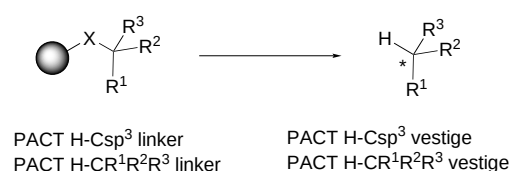
A Solution...

The ultimate function of the linker is to allow cleavage from the support. Regardless of the mechanism of release or the sequence history it will always be possible to define a linker according to the vestigial functionality of the liberated product. A categorization of linkers based on this assertion, where the spotlight falls only on the product functionality created on release from a support, will allow an author simply and precisely to define a linker. Moreover, such a classification should facilitate application to a specific chemical target: a linker may be chosen in light of the desired (or, indeed, tolerable) vestigial functionality—not an easy undertaking at present.

In this article we present such a categorization and, in addition, propose a nomenclature to facilitate its use. The following example is given to illustrate this.

...And a New Nomenclature

In the general transformation depicted in Scheme 1, the linker is cleaved to liberate an alkyl product bearing a hydrogen atom at the former linkage site (marked by an asterisk as it will be throughout this article). The Point of Attachment is Converted To (PACT) an H–Csp³ bond. Hence, the linker illustrated can be described as a PACT H–Csp³ linker or a PACT H–CR¹R²R³ linker.



Scheme 1. An illustration of the nomenclature for a general cleavage transformation where the point of attachment is converted to an alkyl C–H bond: the “PACT H–Csp³” or “PACT H–CR¹R²R³” linker.

Either or both of these descriptors can be used where appropriate; indeed, any expression which accurately describes the molecular structure involved might be used. Central to our approach, however, is the dash representing the bond (–), which indicates the new bond formed to the linking atom or atoms. To the right of the bond is the substrate atom at the former linkage site and to its left is the atom introduced to the substrate at this site.

In terms of the released product, the linker can be accurately defined by the functionalities connected by this new bond. Furthermore, from the complexity or length of this term (which will represent the structural changes incurred on cleavage and any functionality required for cleavage), a broad

assessment of the linker’s generality can be made. By using the same nomenclature the product can be defined in terms of the linker from which it was released by reference to a PACT H–Csp³ vestige or PACT H–CR¹R²R³ vestige.

2. Alkane Formation

2.1. Aliphatic C–H Bond Formation

PACT H–CR₃ or PACT H–Csp³ Linkers

The introduction of an aliphatic hydrogen atom on cleavage from the polymeric support offers arguably the most benign and general vestige: a small, ubiquitous atom, whose influence on biological or chemical activity is minimal. In addition, the linking system expends only one site of molecular diversity. Reports of linkers of this kind which may be classified as PACT H–Csp³ or H–CR₃ linkers are summarized in Table 1, entries 1–3.

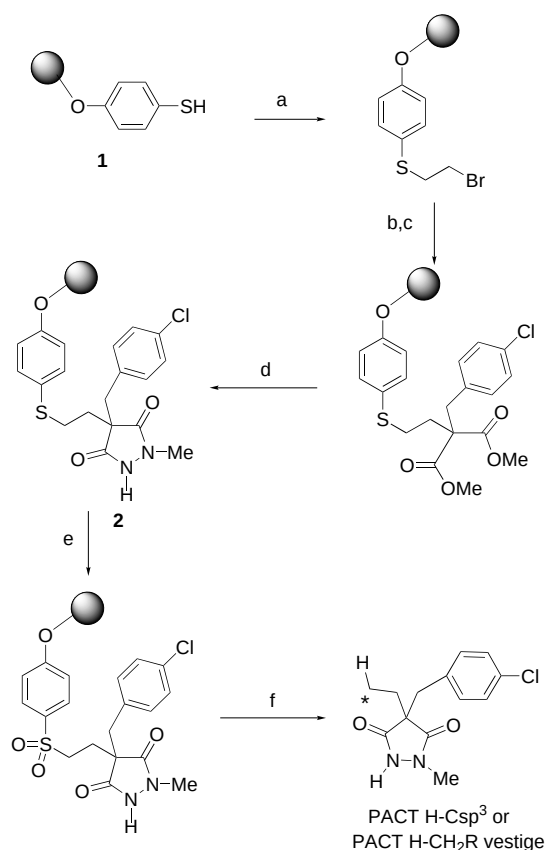
Table 1. Aliphatic C–H and C–C bond formation: PACT H–Csp³ and PACT Csp³–Csp³ linkers.

Entry	Polymeric precursor	Released functionality	Ref.
1		H–CH ₂ R [*]	[2a–h]
2		H–CH ₂ R [*]	[3a,b]
3			[4a–e]
4		R ¹ –CH ₂ –R ² [*]	[5]

An example of a linker of this type (Table 1, entry 1)^[2a–c] is the sulfide system devised by Janda and co-workers (Scheme 2). In an application directed towards the synthesis of a class of heterocycles used in the treatment of rheumatoid arthritis and other diseases thiophenol **1** was alkylated with symmetrical alkyl dihalides. Dialkylation of dimethyl malonate with the polymeric halide and a benzylic halide sets the stage for ester hydrolysis and heterocycle formation with methyl hydrazine to deliver the polymer-bound product **2**. Chemoselective sulfide oxidation with KHSO₅ was followed by reductive release (Na/Hg) of the methyl-bearing product from the PACT H–CH₂R linker.

This approach is not limited to methyl formation (PACT H–CH₂R), but also extends to the mid-chain methylene unit (PACT H–CHR₂).^[2d] Earlier systems from the same research group obviate the thioether oxidation step,^[2e,f] but the Raney nickel hydrogenative cleavage used is clearly incompatible with reduction-sensitive groups such as alkenes, alkynes, or epoxides. Analogous chemistry is reported by Sucholeiki and Forman^[2g,h] in which formation of a benzylic C–H bond accompanies photolytic release.

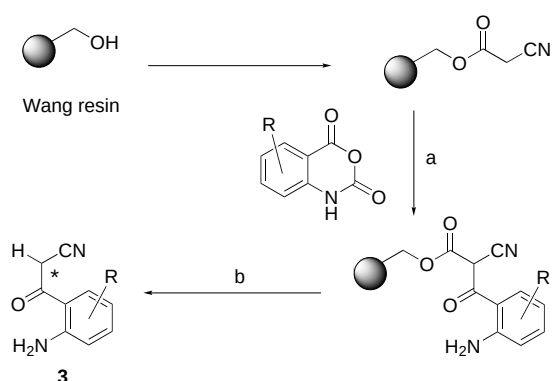
A selenium equivalent is described both by Ruhland et al.^[3a] and Nicolaou et al.^[3b] (Table 1, entry 2) in which a



Scheme 2. PACT H-CH₂R or PACT H-Csp³ linker. Synthesis of 3,5-pyrazolidinediones on polyethylene glycol (PEG) demonstrating polymer cleavage by reductive desulfonylation with sodium amalgam.^[2a-c] a) BrCH₂CH₂Br, Cs₂CO₃; b) CH₂(CO₂Me)₂, Cs₂CO₃; c) *p*-Cl(C₆H₄)CH₂Cl, Cs₂CO₃; d) NaOH, MeNHNH₂; e) KHSO₅; f) Na/Hg, Na₂HPO₄.

haloalkane is directly loaded onto a tethered SeB(OEt)₃⁻Na⁺^[3a] or SeLi^[3b] species. Ruhland et al illustrate the linker's use with the construction of a small library by means of the Mitsunobu reaction. Homolytic cleavage of the Se-C bond was brought about with tributylstannane/azobisisobutyronitrile (AIBN).

Decarboxylative aliphatic C-H bond formation (Table 1, entry 3) can be attributed to Patchornik and Kraus,^[4a] who in 1970 disclosed the monoacylation of tethered esters and decarboxylative release from the support. Ganesan and co-workers have recently demonstrated the principle (Scheme 3)



Scheme 3. PACT H-CHR₂ or PACT H-Csp³ linker. Synthesis of β -ketonitrile displaying a decarboxylative release.^[4b] a) NEt₃; b) 70 % TFA.

with a synthesis of β -ketonitriles **3**.^[4b,c] C-Acylation of the active methylene group precedes a trifluoroacetic acid promoted release and concomitant loss of CO₂.

2.2. Aliphatic C-C Bond Formation

PACT R₃C-CR₃ or PACT Csp³-Csp³ Linkers

An alternative approach to the release of aliphatic systems is the formation of a C-C bond. Schiemann and Showalter described the displacement of products from a benzotriazole linker using Grignard reagents as the carbon nucleophiles (Table 1, entry 4).^[5]

3. Alkene Formation

3.1. Mid-Chain Alkene Formation

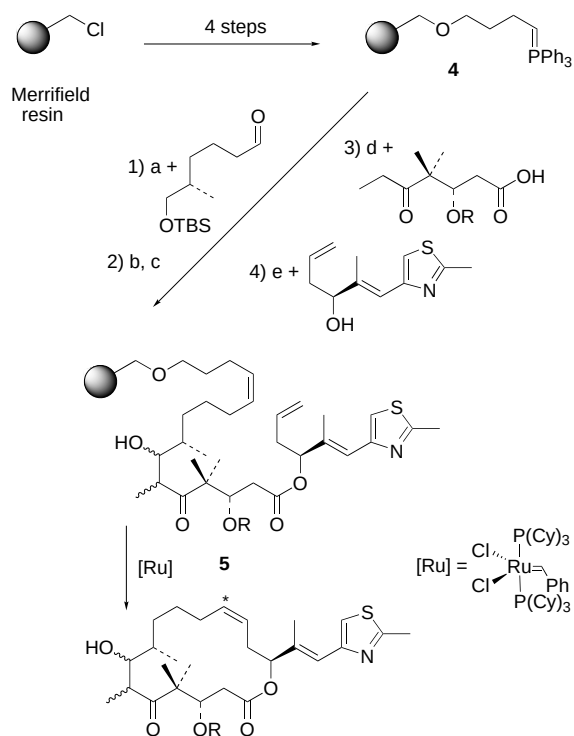
PACT R₂C=CR₂ or PACT Csp²=Csp²(alkene) Linkers

There exists numerous linking methods to achieve a carbon-carbon double bond upon cleavage should this motif be required or tolerable in a product. To date, however, the systems with this capacity are generally more structurally complicated than those described hitherto; between two and four sites of molecular diversity are expended, depending on the process employed. From a different perspective, of course, release can be said to be accompanied by an increase in molecular diversity. The “double” dash in the descriptor for these linkers, PACT R₂C=CR₂, indicates the formation of the double bond in the new alkene.

In a strategy for the solid-phase synthesis of epothilone A Nicolau et al. described a ring-closing metathesis (RCM) approach^[6a] to carbon-carbon double-bond generation on product release (Table 2, entry 1). The structural requirements for RCM, namely two alkene units, are incorporated in a five-step process from the ylide **4** (Scheme 4). Exposure of diene **5** to Grubbs' ruthenium catalyst effects product release and alkene formation. Nicolau et al., in fact, proceeded to epoxidize this functionality, and a substantial library of epothilone analogues has been prepared following this final solution-phase reaction.^[6b] Similar thinking is to be found

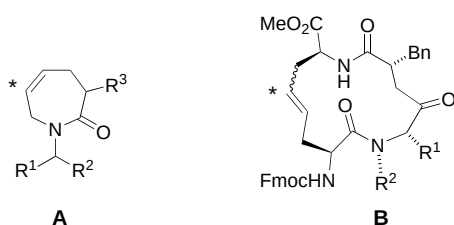
Table 2. Alkene formation: PACT R₂C=CR₂ or PACT Csp²=Csp²(alkene) linkers.

Entry	Polymeric precursor	Released functionality	Ref.
1			[6a-f]
2			[7a,b]
3			[8a-f]
4			[9a,b]



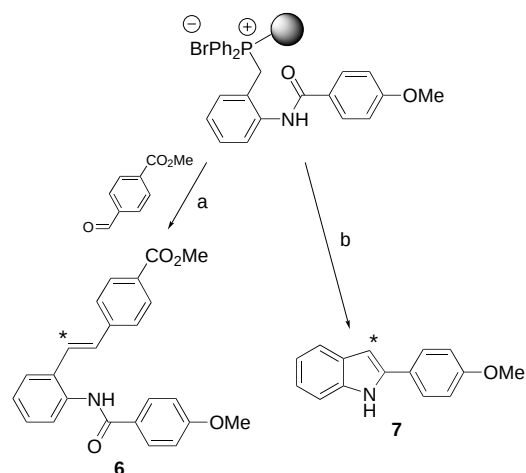
Scheme 4. PACT C=C or PACT Csp²=Csp² linker. Synthesis of epothilone A demonstrating a ring-closing metathesis strategy.^[6a] a) THF; b) HF·Py; c) (COCl)₂, DMSO, NEt₃; d) lithium diisopropylamide (LDA), ZnCl₂; e) *N,N'*-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP). [Ru] = Grubbs' catalyst.

behind the preparation of Freidinger lactams (**A**) by Piscopio et al.^[6c,d] and van Maarseveen et al.^[6e] Blechert and co-workers have also used the process to generate the tetrapeptide-derived macrocycle **B** through a PACT C=C or PACT Csp²=Csp² linker by ring-closing metathesis.^[6f]



Entries 2 and 3 of Table 2 represent the Horner–Wadsworth–Emmons^[7a,b] and Wittig reactions,^[8a–f] respectively. Nicolau et al., for example, have recently reported an intramolecular ketophosphonate reaction which generates macrocyclic lactones and the precursors to a (DL)-muscone library.^[7a] Hughes' phosphonium salt system^[8a] (Scheme 5) is readily available from polymer-bound triphenylphosphane and a benzyl bromide. An intermolecular Wittig reaction affords stilbenes such as **6** whereas intramolecular cleavage to generate indoles of type **7** can be induced under anhydrous conditions.

An allylic sulfone linker created by Kurth and co-workers (Table 2, entry 4) results in the generation of trisubstituted alkenes and cyclobutylidenes.^[9] Nucleophilic displacement of



Scheme 5. PACT C=C or PACT Csp²=Csp² linker. Application of the Wittig reaction to product cleavage and alkene formation.^[8a] a) NaOMe; b) KOtBu.

the products was effected by allylic alkylation with Grignard reagents^[9a] or under milder and more general palladium catalysis^[9b] (PACT RH₂CHCsp²=Csp²R₂).

3.2. Formation of Terminal Alkenes

PACT H₂C=C or H₂Csp²=Csp² and PACT C=CH₂ or Csp²=Csp²H₂ Linkers

Products possessing a terminal alkene functionality are accessible through several linking systems. Not unlike those in the previous section, these also require a high degree of structural complexity for cleavage to occur; unless the structural configurations summarized in Table 3 are specifically sought, these linkers are perhaps less useful than, for example, the PACT H–CR₃ ones.

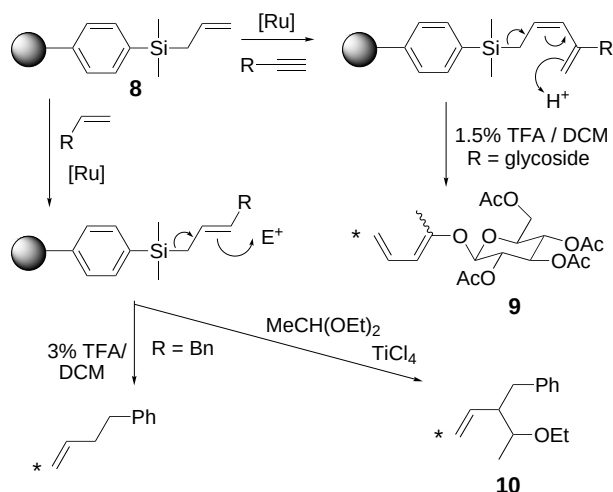
Complementary to RCM cleavage is a system shown in Table 3, entry 1. The product is released bearing the mono-

Table 3. Terminal alkene formation: PACT H₂C=C or H₂Csp²=Csp² and PACT C=CH₂ or sp²=Csp²H₂ linkers.

Entry	Polymeric precursor	Released functionality	Ref.
1			[10a,b]
2			[11a,b]
3			[12a,b]
4			[13a,b]
5			[3b]

substituted alkene (PACT $\text{H}_2\text{C}=\text{C}$) while the product resulting from ring closing remains tethered to the support: Peters and Blechert have thus produced an array of styrene derivatives^[10a] and Knerr and Schmidt have used the linker for the release of oligosaccharides in the form of their 1-*O*-allyl derivatives.^[10b]

Blechert and co-workers have also developed a novel allylsilyl linker strategy that is suitable for electrophilic cleavage (Table 3, entry 2). The allyldimethylsilylpolystyrene resin **8** (Scheme 6) is prepared by the addition of allyldimethylsilyl chloride to lithiated polystyrene and undergoes cross-metathesis using Grubbs' ruthenium catalyst with both

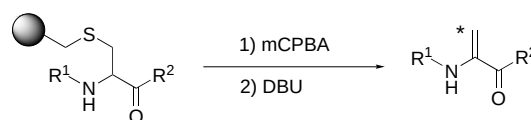


Scheme 6. PACT $\text{C}=\text{CH}_2$ or PACT $\text{Csp}^2=\text{Csp}^2\text{H}_2$ linker. An allylsilyl system which undergoes electrophilic cleavage to produce terminal alkenes^[11b] and dienes.^[11a] [Ru] = Grubbs' catalyst; DCM = dichloromethane.

alkynes^[11a] and alkenes.^[11b] For the former, protodesilylation under extremely mild conditions affords terminal 1,3-dienes such as the glycoside derivative **9**. Formation of a further C–C bond on product release is also viable: cross-metathesis of **8** with an alkene followed by addition of the electrophile derived from 1,1-diethoxyethane and TiCl_4 delivers **10**.^[11b]

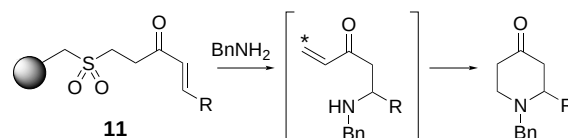
In a third approach proposed by the same research group (Table 3, entry 3) the vestigial functionality after cleavage is also the functionality required for cleavage to take place. Further structural diversity is introduced during a palladium(0)-catalyzed nucleophilic cleavage.^[12a] The reaction with both carbon and nitrogen nucleophiles has been demonstrated: Brown and Fisher, in fact, have generated pyrrolidines through cyclization with a pendant secondary amine as the nucleophile.^[12b]

β -Elimination of a sulfone prepared by oxidation of a sulfide tether (Table 3, entry 4) can also afford a terminal alkene. Yamada et al. have applied this technology to a synthesis of dehydroalanine derivatives (Scheme 7).^[13a] Both the N- and C-termini of the tethered cysteine residue remain open for modification, and the intermediate sulfide linker is robust to most reaction conditions; oxidation, of course, provides the sulfone which readily undergoes elimination in the presence of a base.



Scheme 7. PACT $\text{C}=\text{CH}_2$ or PACT $\text{Csp}^2=\text{Csp}^2\text{H}_2$ linker. Sulfone elimination delivers dehydroalanine derivatives.^[13a] mCPBA = *m*-chloroperbenzoic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

A series of substituted piperidin-4-ones was similarly prepared by Barco et al.^[13b] whose enones **11** (Scheme 8) undergo a Michael addition with benzylamine. The resultant tethered secondary amine induces elimination and release,



Scheme 8. PACT $\text{C}=\text{CH}_2$ or PACT $\text{Csp}^2=\text{Csp}^2\text{H}_2$ linker. Synthesis of piperidine-4-ones: benzylamine effects sulfone elimination and a tandem aza-Michael addition.^[13b]

and the desired product is isolated after a second, solution phase, Michael addition to the liberated enone. Although not implicit in the isolated piperidinone product, the specific linker depicted in Scheme 8 is most practicably described in terms of the alkene it releases into solution (PACT $\text{C}=\text{CH}_2$). That the alkene is an intermediate which participates in a further solution-phase transformation reflects the imagination of the authors and not the general chemistry of the linker.

The selenium linker described by Nicolaou et al. in Section 2.1 has also been applied, under different cleavage conditions (hydrogen peroxide solution), to the oxidative release of terminal alkenes (Table 3, entry 5).^[3b]

4. Alkyne Formation

PACT $\text{Csp}\equiv\text{Csp}$ or PACT $\text{RC}\equiv\text{CR}$ Linker

Until recently there existed no linking technology with the capacity to release alkyne functionality on cleavage. In a novel approach to a protecting group linker of Type C (see Figure 1) Gibson and co-workers describe the immobilization of alkyne substrates to polymer-bound triphenylphosphane through π interactions to dicobalt carbonyl complexes (Table 4). The products are liberated by aerial oxidative decomplexation with a PACT $\text{Csp}\equiv\text{Csp}$ vestige.^[14]

Table 4. Alkyne formation: PACT $\text{C}\equiv\text{C}$ or PACT $\text{Csp}\equiv\text{Csp}$ linker.

Entry	Polymeric precursor	Released functionality	Ref.
1		$\text{R}^1-\text{C}\equiv\text{C}-\text{R}^2$	[104]

5. Arene and Heteroarene Formation

5.1. Aromatic C–H Bond Formation

PACT H–Csp²(arene) Linkers

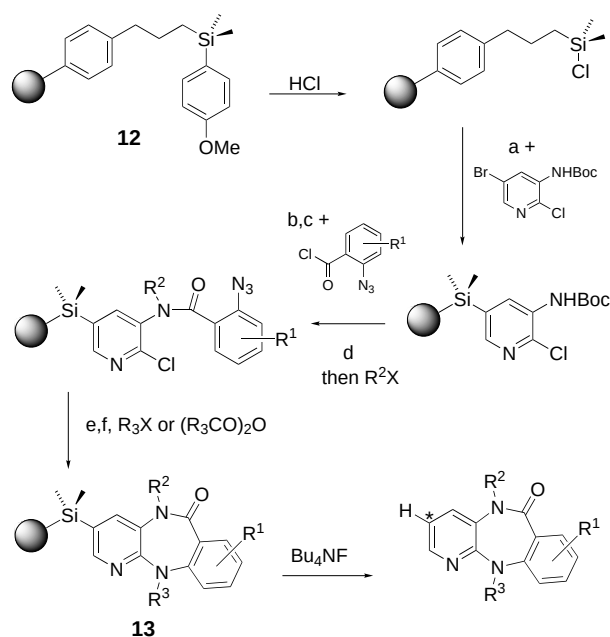
Extremely prevalent in organic compounds is the arene or heteroarene system, and the literature details a variety of linkers which release a compound bearing an aromatic C–H bond as the only vestige of the support. Analogous in many ways to those described for alkyl C–H bond formation, these systems expend only one site of molecular diversity and have been applied to phenyl, pyridine, thiophene, and quinazoline substrates.

The seminal report of Plunkett and Ellman of a silicon-based system^[15a] (Table 5, entry 1) continues to inspire much

Table 5. Aromatic C–H bond formation: PACT H–Csp²(arene) linkers.

Entry	Polymeric precursor	Released functionality	Ref.
1			[15a–q]
2			[16]
3			[17a–c]
4			[18a,b]
5			[19]

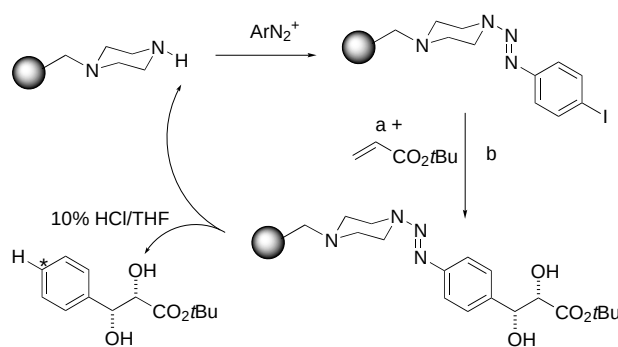
research;^[15b–q] an example of their work is represented in Scheme 9.^[15b] The stable silyl resin **12** is readily prepared in two steps from bromophenyl-substituted polystyrene; activation by brief exposure to HCl/CH₂Cl₂ gives an unmasked silyl chloride which will undergo coupling with a metalated arene derivative. Three elements of diversity are incorporated by means of the addition of 2-azidobenzoyl chloride, amide alkylation, and, following reduction with azide and tricycle formation, a second N-alkylation. Cleavage of the tethered product **13** and aromatic C–H bond formation is accomplished with tetrabutylammonium fluoride (TBAF). (The silicon system has also been translated from the solid to the fluorous phase.^[15p,q] Curran and co-workers have described the Ugi and Biginelli multicomponent condensations for the preparation of fluorine-tagged benzoylated amino acid amides.^[15q] Desilylation was effected with TBAF, followed by separation of the arene product with a simple liquid–liquid extraction.)



Scheme 9. PACT H–Csp²(arene) linker. Synthesis of pyridine-based tricycles using a silicon linker for aromatic C–H bond formation.^[15b] a) KH, BuLi; b) TFA; c) DCM, Py; d) lithiated acetanilide; e) SnCl₂, PhSH, NEt₃; f) TFA. Boc = *tert*-butoxycarbonyl.

Alternative conditions for the release from the support include treatment with 30–50 % trifluoroacetic acid (TFA) in CH₂Cl₂^[15c–f] or neat TFA.^[15g,h] An electron-poor arene, however, requires extremely forcing conditions to effect *ipso* electrophilic substitution of silicon: anhydrous HF gas was applied by Plunkett and Ellman^[15i] to the release of a benzodiazepine substrate. Replacement of silicon with the less acid-stable germanium derivative,^[15i,j] though rather expensive, is one solution to this problem. Another solution, however, is offered by Wustrow and co-workers (Table 5 entry 2):^[16] The aryl sulfonate system undergoes efficient Pd(0)-catalyzed reductive cleavage with electron-poor arenes.

An attractive linker is depicted in Table 5, entry 3.^[17a–c] Not only robust and somewhat more accessible than the silicon linkers so far reported, it liberates the regenerated resin upon product release. The piperazine resin depicted in Scheme 10



Scheme 10. PACT H–Csp²(arene) linker. A system boasting a recyclable resin for aromatic C–H bond formation.^[17a] a) Pd(OAc)₂, PPh₃, NEt₃, DMF; b) AD-mix β.

undergoes coupling with the arene diazonium salts derived from primary aromatic amines. A variety of Heck reactions and subsequent chemistry on the unsaturated substrate (including asymmetric dihydroxylation, Diels–Alder reactions, and palladium-catalyzed allylic substitution) have been carried out. Cleavage of the triazene with aromatic C–H bond formation was effected with acid. A similar linking system (Table 5, entry 4) from which release occurs by alcoholysis or aminolysis is an aryldiazene which is formed prior to cleavage by the oxidation of the arylhydrazide.^[18a,b]

The decarboxylative C–H bond formation detailed in Section 2 has also been applied to an aromatic substrate (Table 5, entry 5).^[19]

Interestingly, an additional facet of the arylsilane, arylgermane, and triazene linkers described above (Table 5, entries 1 and 3) is cleavage by electrophilic *ipso*-halogenation using ICl, Br₂, or NCS to obtain iodides, bromides, or chlorides, respectively (PACT X–Csp²(arene)).

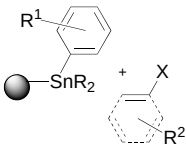
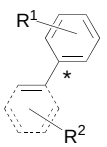
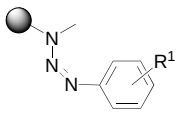
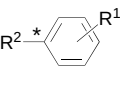
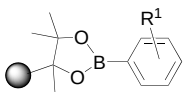
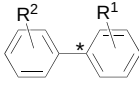
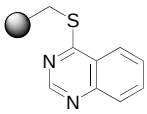
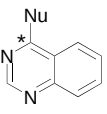
5.2. Aromatic C–Csp² Bond Formation

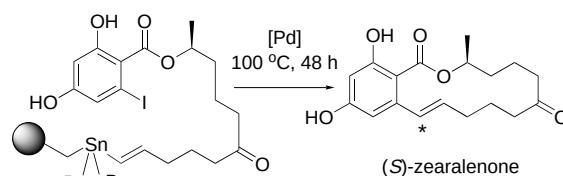
PACT C–Csp²(arene) Linkers

The formation of a C–C bond on cleavage of a product from the resin does, perhaps, have advantages over simple C–H bond formation, in that a further degree of diversity is incorporated.

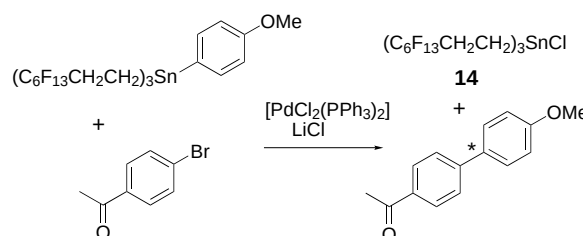
The Stille coupling reaction (Table 6, entry 1) has been applied to just this transformation.^[20a–c] The system will not only deliver the styryl functionality as demonstrated by the synthesis of (*S*)-zearelenone by Nicolaou et al. (Scheme 11),^[20a] but is equally well suited to diene, enyne, or biaryl formation.^[20b] The fluorous phase approach also accommodates this chemistry very elegantly: Curran and Hoshino have prepared a variety of biaryls according to Scheme 12, wherein the tin chloride **14** is recovered in high yield and re-used following a simple extraction.^[20c]

Table 6. Aromatic C–Csp² bond formation: PACT C–Csp²(arene) linkers.

Entry	Polymeric precursor	Released functionality	Ref.
1			[20a–c]
2			[21a,b]
3			[22]
4			[23]



Scheme 11. PACT Csp²(arene)–Csp²(alkene) linker. A Stille coupling methodology resulting in diene or styrene derivatives on release.^[20a]



Scheme 12. PACT Csp²(arene)–Csp²(arene) linker. Fluorous-phase synthesis of biarenes using the Stille coupling reaction.^[20c]

A Heck cross-coupling strategy using the triazene linker seen previously for aromatic C–H bond formation (see Table 5, entry 3) has been equally successful (Table 6, entry 2).^[21a,b] Suzuki coupling has been applied to the macrocyclization/cleavage of β -turn mimetics containing a biaryl component (Table 6, entry 3).^[22]

Nucleophilic displacement of a thioether tether from a quinazoline nucleus also results in aromatic Csp²–C bond formation (Table 6, entry 4). Using such a linker Hennequin and Piva-Le Blanc have prepared oxindole quinazolines, which constitute a novel series of tyrosine kinase inhibitors.^[23]

5.3. Aromatization

PACT Csp²–Xsp² and Xsp²–Csp²(arene/heteroarene) Linkers

Numerous linking technologies have been elaborated for which product release is driven by an aromatization process (Table 7).

Employing a resin-bound *o*-quinodimethane (Table 7, entry 1) Craig et al. have demonstrated the principle in the synthesis of naphthalene and isoquinoline derivatives by means of both homo- and hetero-Diels–Alder reactions with dimethylacetylene dicarboxylate, benzoquinone, and trichloroacetonitrile as dienophiles.^[24]

Analogous to the PACT Csp≡Csp linker described in Section 4, arenes have been immobilized onto a resin-bound phosphane through π interactions to a chromium dicarbonyl complex (Table 7, entry 2).^[25] The (η^6 -arene)-tricarbonyl chromium complexes are polymer-loaded under photolytic conditions and, following substrate manipulation, are released on decomplexation by aerial oxidation or refluxing pyridine.

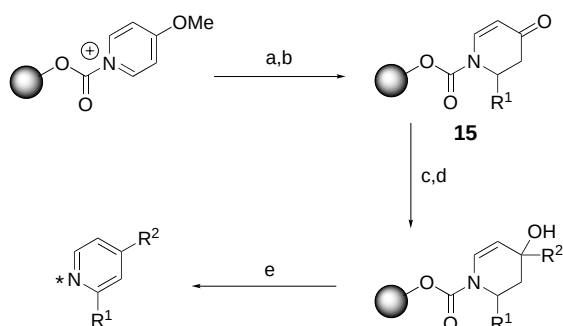
The preparation of isoquinoline-based compounds is represented by entry 3 of Table 7. The precursor to release is formed when resin-bound benzoyl chloride is treated with isoquinoline and trimethylsilyl cyanide (TMSCN); subsequent alkylation at C1 is a facile process and the product is released with a KOH-promoted Reissert hydrolysis. The

Table 7. Arenes released on aromatization: PACT Csp²–Xsp² and PACT Xsp²–Csp²(arene/heteroarene) linkers.

Entry	Polymeric precursor	Released functionality	Ref.
1			[24]
2			[25]
3			[26a,b]
4			[27]
5			[28]
6			[29]
7			[30a,b]

linker is stable to isoxazoline formation^[26a] and Suzuki coupling.^[26b]

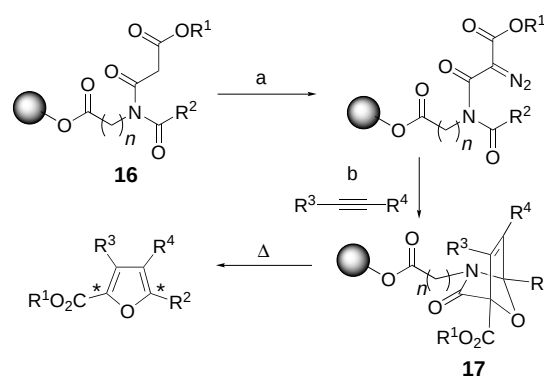
A technology proposed by Chen and Munoz (Table 7, entry 4) allows for the functionalization of pyridine analogues.^[27] Successive alkylations, first to form the dihydropyridone **15** (Scheme 13) and then a 1,2-addition using an organocerium reagent afford an enamide alcohol, which, when treated with acid under oxidative conditions, aromatizes to release the product (PACT Csp²–Nsp²(pyridine)).



Scheme 13. PACT Csp²–Nsp²(pyridine) linker. Regioselective alkylations and an oxidative cleavage release of a pyridine derivative bearing no additional vestige of the polymer.^[27] a) R¹MgX; b) H₃O⁺; c) CeCl₃, R²MgX; d) H₃O⁺; e) TFA, O₂.

In a further demonstration of its versatility, the triazine linker seen twice previously favors cyclization in the presence of a suitable nucleophilic *ortho* substituent. Bräse et al. applied such thinking to the cyclization and release of cinnolines (Table 7, entry 5), wherein triazine-bound *ortho*-alkynylarenes were cyclized with aqueous HCl or HBr.^[28] Not dissimilar is the acid-mediated cyclorelease of 3-aminobenzisoxazoles which has been shown to take place from the aryloxime polymeric precursor shown in Table 7, entry 6.^[29]

The system depicted in Table 7, entry 7 allows for the liberation of tetrasubstituted furans by means of a cycloreversion/aromatization process.^[30] The synthesis is illustrated in Scheme 14:^[30b] diazotransfer of substrate **16**, synthesized on Wang resin in two steps, results in the diazoester onto which the rhodium(II)-mediated 1,3-dipolar cycloaddition with activated acetylenes is carried out. The cycloadduct **17** is isolable at ambient temperature such that cleavage may be effected by heating.



Scheme 14. PACT Csp²–Csp²(furan) linker. Rhodium(II) perfluorobutyramide (pfbm) mediated 1,3-dipolar cycloaddition and cycloreversion/aromatization to release furans.^[30b] a) MsN₃, NEt₃; b) Rh₂(pfbm)₄.

6. Amine Formation

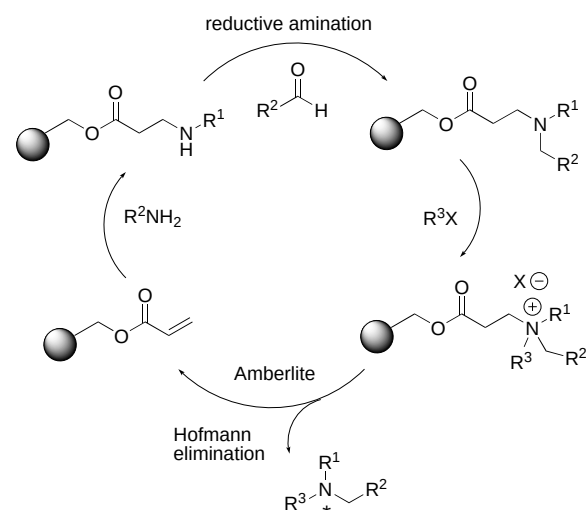
PACT NR₃, PACT R¹–NR²R³, and PACT (H–)₃CNR₂ Linkers

The incorporation of an amine on release from the resin may be effected in a variety of ways. Tertiary amines are a particularly widespread functionality in terms of drug discovery, and in particular are commonly found in drugs active within the central nervous system.

Entry 1 of Table 8 portrays an eliminative release first developed by Rees and co-workers:^[31a–g] the absence of a dash from the descriptor for linkers of this kind (PACT NR₃) is indicative of a reduction in the nitrogen valence on cleavage (linker type B, Figure 1). The quaternary amine salt is constructed stepwise: first by an aza-Michael addition of a secondary amine to an acrylate-tethered resin and then quaternization with an alkyl halide allows for a Hofmann elimination in the presence of base, with the acrylate resin being regenerated in high purity. Murphy has elaborated the process by means of a reductive amination after the initial Michael addition (Scheme 15).^[31c] Elimination is promoted by the ion-exchange resin Amberlite and a simple filtration from this novel two-resin system affords the products without need of further purification. Vinyl sulfone systems which operate

Table 8. Amine formation: PACT NR₃, R¹-NR²R³, and (H-)₃CHR₂ linkers.

Entry	Polymeric precursor	Released functionality	Ref.
1			[31a–g]
2			[32a–c]
3			[33a–c]
4			[34a,b]
5			[35a–c]
6			[36a–d]
7			[37]
8			[38]
9			[39]


 Scheme 15. PACT NR₃ or Nsp³ linker. Hofmann elimination of the product follows a three-step construction of the amine through aza-Michael addition, reductive amination, and quaternization.^[31c]

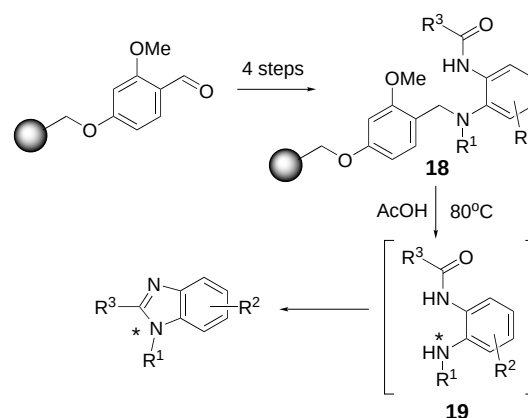
similarly, exhibit high stability to such nucleophiles as Grignard reagents^[31f] and the conditions for Mitsunobu esterification.^[31g]

A sulfonate resin has also been employed in the formation of a tertiary amine (Table 8, entry 2).^[32a–c] The tether, formed from an arylsulfonyl chloride resin and an alcohol, has

demonstrated a tolerance to wide-ranging chemistries including Grignard additions, Wittig reactions, sodium borohydride reduction, reductive amination, and Suzuki coupling.^[32b] Nucleophilic displacement by the amine-forming heteroatom incorporates a further element of diversity (PACT R-NR₂). Alternative nucleophiles such as azide, iodide, or acetate (PACT X-Csp³) enable additional cleavage conditions to be used.^[32d]

In a similar vein, pyridazines have been released from a thiophenyl tether by an S_NAr displacement using primary and secondary amines,^[33a] and pyrimidines have been constructed on a sulfide linker. Oxidation to the sulfone permits nucleophilic displacement (Table 8, entry 3).^[33b,c] A novel application of the carbamate tether is shown in entry 4 of Table 8: reduction with lithium aluminum hydride reveals a latent N-methylamine.^[34a,b] In this case, the valences of the carbon atom involved in the linkage (indicated by the asterisk as before) are replaced by hydrogen atoms during reduction (PACT (H-)₃CNR₂). Cleavage of the linkers which follow proceeds by substitution of the nitrogen valence. More conventionally, therefore, the same carbamate can be cleaved by hydrolysis to liberate primary or secondary amines (Table 8, entry 5; PACT H-NR₂).^[35a–c]

Amines attached to a benzylic carbon atom with the ability to stabilize a cation can be released under acidic conditions. Several such linkers possessing *ortho*- and *para*-alkoxy substituents, the Rink amide linker being one example, have been developed (Table 8, entry 6).^[36a–d] A synthesis of benzimidazoles using a linker of this kind is summarized in Scheme 16. Resin-bound substrate **18**, formed in four steps from the aldehyde resin, undergoes cyclization to give the product heteroarenes (anilines **19**; PACT H-NHAr) via a solution-phase intermediate.


 Scheme 16. PACT H-NHAr or H-Nsp³ linker. Release of **19** and solution-phase cyclization/aromatization to afford benzimidazoles.^[36a]

The acetal-derived linker in entry 7 of Table 8 has been applied to the release of indoles;^[37] cleavage is effected in excellent yield and purity by hydrolysis and subsequent treatment with 2N NaOH. A resin based on a tetrahydropyranyl (THP) protecting group for the linkage of substrates through an aминаl (Table 8, entry 8)^[38] is base stable and cleaved with weak acid. This is true also of the multifaceted

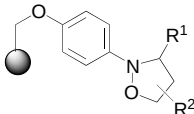
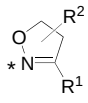
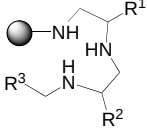
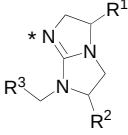
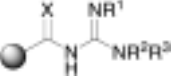
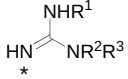
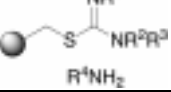
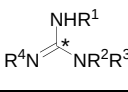
triazene linkage reported by Bräse et al. (Table 8, entry 9)^[39] which enables the release of arenes (see Tables 5 and 6) and heteroarenes (see Table 7).

7. Formation of an Unsaturated Nitrogen Group

PACT $R_2C=NR$ or $Csp^2=Nsp^2$ (isoxazoline/guanidine) and $PACT R^1N=CR^2R^3$ (guanidine) Linkers

Kobayashi and Akiyama have demonstrated the 1,3-dipolar cycloaddition reaction of tethered nitrones with alkenes to form the precursor depicted in entry 1 of Table 9. Oxidative

Table 9. Formation of an unsaturated nitrogen group: $PACT R_2C=N$ and $R_2Csp^2=Nsp^2$ (isoxazoline/guanidine) linkers as well as the $N=CR_2$ (guanidine) linker (entry 4).

Entry	Polymeric precursor	Released functionality	Ref.
1			[40]
2			[41]
3			[42a–c]
4			[43]

cleavage delivers the 2-isoxazoline derivatives.^[40] Another example representative of this linker type is described by Houghton and co-workers.^[41] The exhaustive reduction of resin-bound *N*-acylated dipeptides forms the cleavage precursor in entry 2 of Table 9. Treatment with thiocarbonyldiimidazole results in the *N*-tethered bicyclic guanidine which is liberated using hydrogen fluoride. Guanidines have also been liberated by more conventional means: an amide-derived linkage, drawn schematically in entry 3 of Table 9 can be cleaved under acidic conditions^[42a–c] and an isothiourea has been cleaved by aminolysis (Table 9, entry 4).^[43]

8. Formation of Carboxylic Acid Derivatives

Carboxylic acid derivatives, which form the basis of solid-phase peptide synthesis and have led to the development of novel linking technologies, are the antithesis of “tracelessness”. A comprehensive survey of this expansive area is inappropriate here; important details, however, such as resin type, linkers, and cleavage conditions are fully documented in several excellent reviews.^[1] The following section uses selected developments to illustrate the PACT approach.

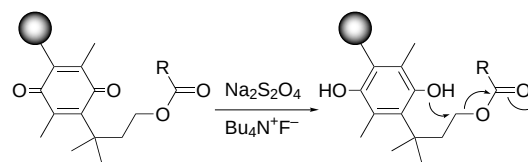
8.1. Formation of Carboxylic Acids

PACT $H-O_2CR$ and $PACT HO-C(O)R$ Linkers

Classically, immobilization of a growing peptide chain by means of an ester link to the C-terminus of an amino acid led to the liberation of a carboxylic acid on acid hydrolysis: $PACT H-O_2C$ vestige. Merrifield's benzylic esters required the very strong acid HF and early improvements such as the Wang (50 % TFA) or Sasrin linkers (1 % TFA) were achieved by modulating the electron density of the linker's phenyl ring.

Recent examples which make use of the Wang linker include the construction of polyheterocyclic compounds through Diels–Alder reactions by Sun and Murray^[44a] and the synthesis of bicyclo[2.2.2]octane derivatives through tandem Michael addition reactions by Ley et al.^[44b] Gallop and co-workers have successfully involved the Sasrin linker in a combinatorial synthesis of highly functionalized monocyclic β -lactams.^[44c]

An alternative cleavage strategy to access carboxylic acids employs the so-called “safety-catch” linkers: Hulme et al. have described a Boc activation of a benzamide linker^[45a] immediately prior to cleavage with LiOH ($PACT HO-C(O)$), and Backes and Ellman have employed Kenner's acylsulfonamide linker^[45b] which is stable under basic conditions but activated to nucleophilic displacement with LiOH by *N*-methylation with diazomethane. Along similar lines, an unusual linking device possessing the redox-sensitive *p*-benzoquinone core (Scheme 17) cyclizes on reduction to the hydroquinone to expel the acid.^[45c] The mild reduction and base-catalyzed formation of the cyclic ether (using $Na_2S_2O_4$ and $Bu_4N^+F^-$, respectively) provide an alternative procedure where acid conditions are undesirable.



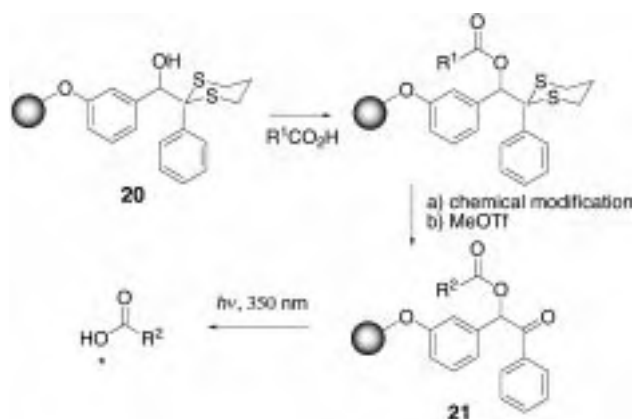
Scheme 17. $PACT H-O_2C$ linker. Reduction to the hydroquinone and base-catalyzed formation of a cyclic ether effect expulsion of the product.^[45c]

A wide variety of photolabile supports, which are commonly based on the *o*-nitrobenzyl moiety,^[46a] also release carboxylic acids. Lee and Balasubramanian report a novel example (Scheme 18) in which a diisopropylcarbodiimide coupling of a carboxylic acid to dithiane derivative **20** allows for subsequent chemical manipulation of the substrate on the solid phase.^[46b] The dithiane unit, which acts as a “safety catch” against premature photorelease, is removed by alkylation with methyl triflate to afford photolabile linker **21** from which the product is released in excellent yield.

8.2. General Amide Formation

PACT $N-C(O)$ and $PACT H-NC(O)$ Linkers

Amide bond formation has been thoroughly optimized throughout the years and is consequently used extensively in



Scheme 18. PACT H–O₂C linker. Photorelease from a benzoin system employing a dithiane “safety-catch”.[46b]

solid-phase methodologies and combinatorial synthesis. It is integral to the pharmacophore of a multitude of therapeutic drugs, and is found not only in its simple form but also in numerous guises (Table 10).

8.2.1. Formation of Acyclic Amides

The release of simple linear amides, such as **22** (Table 10), is thoroughly documented: well-established protocols such as the acidic cleavage of an amide from the Rink amide resin[47a–d] and photorelease from an *o*-nitrobenzyl linker[44c] can be defined as PACT H–NC(O). Aminolysis of an ester[44b, 47e–n] or of linkers based on *N,N*-methylacrylsulfonamide (Kenner’s “safety-catch”)[45b, 47o,p] give secondary or tertiary amides (PACT N–C(O)). Ureas **23** (Table 10) are accessible by aminolysis of resin-bound carbamates[48a–d] and hydroxamic acids **24** (Table 10) by aminolysis of esters with hydroxylamine.[49a,b] Proteolytic release from an immobilized trityl[49c–e] or *p*-alkoxybenzyl[49f–h] hydroxamate also gives hydroxamic acids (PACT H–ON(H)C(O) or PACT RON(–H)C(O)[49h]).

An interesting variant is the acylative dealkylation of resin-bound tertiary benzylamines with acid chlorides[47q] or chloroformates.[47r] The latter are examples of linker type B (see Figure 1), wherein release occurs from an electron-rich benzyl tether after quaternization of the linking amide nitrogen atom (PACT RRNC(O)). Along similar lines, a particularly versatile linking system which releases a variety of functionalities of this kind is reported by Estep et al. (Scheme 19).[47s] Primary amines are linked to the resin by means of an indole and immobilized by the reductive amination of a resin-bound aldehyde. Subsequent reaction with various electrophiles (carboxylic acids, isocyanates, chloroformates, or sulfonyl chlorides) forms tethered secondary amide derivatives which are liberated as primary derivatives (amides **22**, ureas **23**, carbamates **25**, or sulfonamides, respectively) on treatment with 2–5 % TFA in CH₂Cl₂.

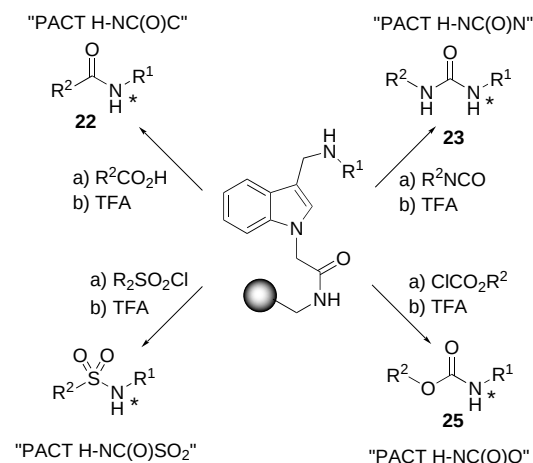
8.2.2. Formation of Cyclic Amides

With few exceptions, cyclic amidic structures are liberated from a solid support by lactamization; this comes as a direct

Table 10. General formation of amides: Acyclic and cyclic products accessible with PACT H–NC(O) and N–C(O) linkers.

Amidic structure	Formula number and ref.
	22 [44b,45b,47a–s]
	23 [47s,48a–d]
	24 [49a–h]
	25 [47r,s]
	26 [50a–i]
	27 [51a–g]
	28 [52a–c]
	29 [53]
	30 [54a–c]
	31 [55a–m]
	32 [56a–d]
	33 [57a–d]
	34 [58]

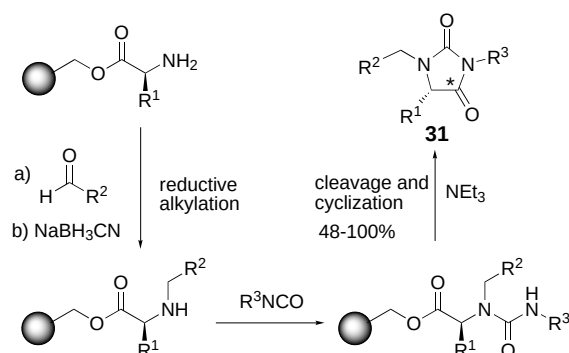
result of the most deeply rooted solid-phase peptide synthesis protocol whereby an amino acid or derivative is immobilized through the C-terminus. A pendant NH functionality of the linear product precursor consequently effects an intramolecular cleavage of the ester linkage to create the amide vestige (PACT N–C(O)). Numerous systems of this kind are to be



Scheme 19. A versatile support for the release of amide functionalities.^[47s] Amides, ureas, carbamates, and sulfonamides are accessible.

found for every heterocycle listed in Table 10: diketopiperazines **26**,^[50a-i] cyclic peptides **27**,^[51a-g] lactams **28**,^[52a-c] benzodiazepines **29**,^[53] 1,4-benzodiazepine-2,5-diones **30**,^[54a-c] hydantoin **31**,^[55a-m] quinazoline-2,4-diones and pyrimidine-2,4-diones **32**,^[56a-d] pyrazolones **33**,^[57a-d] and 3H-quinazoline-4-ones **34**.^[58]

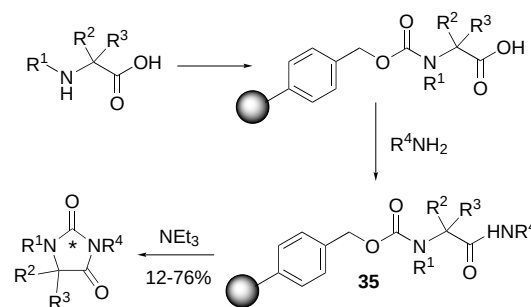
An example representative of the general methodology is detailed in Scheme 20.^[55c] Matthews and Rivero describe a



Scheme 20. PACT N-C(O)(hydantoin) linker. The amino acid is attached at the C-terminus through an ester tether. The amide functionality is incorporated through cleavage and cyclization.^[55c]

synthesis of 1,3,5-trisubstituted hydantoins which takes advantage of the host of commercially available amino acids, primary amines, and aldehydes. Scheme 20 depicts the reductive alkylation of a C-terminus-bound α -amino acid with aldehydes, acylation of the secondary amine with an isocyanate to generate an acyclic urea precursor, and base-promoted cleavage and cyclization to give the product **31** in moderate to quantitative yield.

However, other strategies for the liberation of a cyclic amide have been employed. Immobilization of an amino acid or derivative at the N-terminus through a carbamate linker presents a scaffold that is also set for lactamization on cleavage; cyclic peptides **27**,^[51e] quinazoline-2,4-diones **32**,^[56c,d] and hydantoins **31**^[55j] have been isolated in this way. The system illustrated in Scheme 21 can be compared to that in



Scheme 21. PACT N-C(O)(hydantoin) linker. The amino acid is connected at the N-terminus through a carbamate tether. The amide functionality is then incorporated through cleavage and cyclization.^[55j]

Scheme 20. The coupling of the N-terminus of an amino acid to an activated carbonate resin followed by standard elaboration to give the linear substrate **35** sets the stage for a base-induced cleavage and cyclization of the carbamate tether.^[55j]

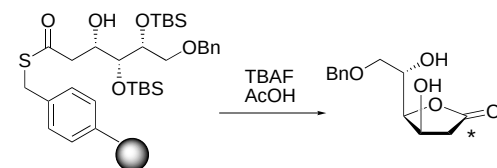
8.3. Formation of Esters and Lactones

PACT O-C(O) or PACT O=C(OR) Linkers

Esters^[45a, 59a-f] and lactones^[60a-h] are analogous in many ways in terms of their release from a solid support to the amides already discussed. Alcoholysis of simple esters^[59a] and silyl esters^[59b] (transesterification) or of amides^[45a, 59c] has been used to liberate acyclic esters (PACT RO-C(O)R).

Another widely used protocol is the formation of acetates from substrates bound through a benzyl ether linker by a Lewis acid (ZnBr_2) catalyzed reaction with acetyl bromide.^[59d] Similarly, 1-O-acetyl glycosides are released from a glycosyl ether tether with $\text{Ac}_2\text{O}/\text{BF}_3 \cdot \text{OEt}_2$.^[59e,f]

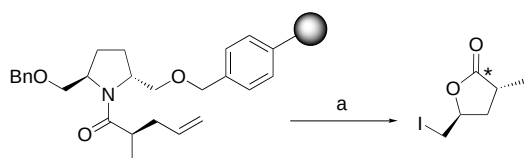
Kobayashi et al. have developed an intramolecular solid-phase synthesis of monosaccharide derivatives (Scheme 22)^[60a] whereby a thioester tether is cleaved by a pendant



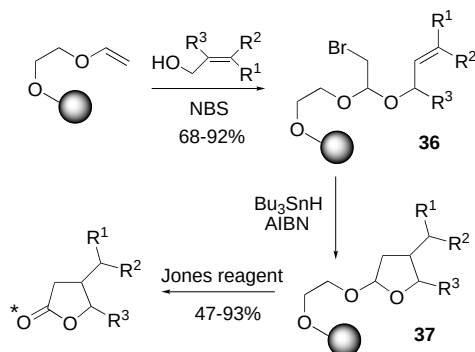
Scheme 22. PACT O-C(O)(lactone) linker. Monosaccharide synthesis with a lactonization/cleavage step.^[60a]

hydroxy group. Homoserine lactones^[60b] and phthalides^[60c] have been prepared using the same concept, whereby lactonization cleaves an amide linker. Cyclorelease of oxazolidinones^[60d] and γ - and δ -lactones^[60e] has also been induced by nucleophilic ring opening of epoxides prepared on the solid phase. A variation on this theme is given by Kurth and co-workers (Scheme 23). High diastereoselectivity is induced by a "C₂-symmetric" pyrrolidine-based tether during the course of an iodolactonization.^[60f,g]

Using a different release strategy, the oxidation of resin-bound cyclic acetals using the Jones reagent also serves to liberate γ -lactones (Scheme 24).^[60h] A series of β -bromoace-



Scheme 23. PACT O-C(O)(lactone) linker. Iodolactonization with a pyrrolidine-induced diastereoselectivity.^[60g] a) I₂, THF, H₂O, *tert*-butyldimethylsilyl.



Scheme 24. PACT O=C(OR)(lactone) linker. Radical cyclization and an oxidative release.^[60h]

tals **36** was prepared by treatment of the immobilized vinyl ether with allyl alcohols in the presence of *N*-bromosuccinimide (NBS). Radical cyclization, a process rarely exploited on the solid phase, proceeded efficiently with Bu₃SnH/AIBN to give only the 5-membered lactone precursor **37**. The products were isolated in high yield following oxidative release (PACT O=C(R)OR).

9. Aldehyde Formation

PACT H-C(O)R and PACT O=CHR Linkers

The release of the aldehyde functionality is relatively undeveloped on the solid phase, and has been primarily directed towards the synthesis of C-terminal peptide aldehydes, which are of interest as inhibitors of several classes of enzymes. Five distinct approaches are summarized in Table 11.

Aldehydes have been formed by reduction of a tether based on the Weinreb amide with lithium aluminum hydride (Table 11, entry 1; PACT H-C(O)R).^[61a,b] The preparation of small, non-peptidic molecules using the same methodology is also described,^[61c,d] but yields are generally low and problems associated with purification and racemization are important considerations, especially in peptide synthesis.

The resin-bound product precursor in entry 2 of Table 11 is attached by an alkenyl tether, ozonolysis of which liberates the aldehyde product PACT O=C(H)R.^[62a-d] Ozonolytic release is a very clean methodology which proceeds without detectable racemization of a peptidic substrate, and hence has clear advantages over the system detailed in entry 1 of Table 11. Not dissimilar is the oxidative cleavage of the tether based on tartaric acid (Table 11, entry 3).^[63] The 1,2-diol moiety, protected as an acetonide during chemical manipulation of the substrate, is cleaved using sodium periodate to release α -ketoaldehyde derivatives.

Table 11. Aldehyde formation: PACT H-C(O)R or O=CHR linkers.

Entry	Polymeric precursor	Released functionality	Ref.
1			[61a-d]
2			[62a-d]
3			[63]
4			[64a-e]
5			[65]

General protecting group chemistry has also been applied to the immobilization of aldehydes in the form of their acetals^[64a-d] or oxazolidine derivatives^[64e] (Table 11, entry 4); cleavage is effected by acid hydrolysis. A tether based on a semicarbazone derivative has also been described (Table 11, entry 5),^[65] but the system suffers from two drawbacks: the linker is preformed in solution prior to loading onto the resin and the products are liberated with formaldehyde.

10. Ketone Formation

PACT R¹-C(O)R² and PACT O=CR¹R² Linkers

The ketone is a widespread functionality in organic compounds, be it found in its simple form, in conjugation with an unsaturated carbon backbone, or as the enol tautomer. The various methods by which it can be achieved are summarized in Table 12.

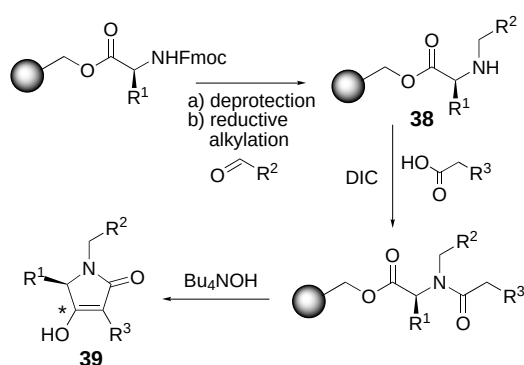
Table 12. Ketone formation: PACT R¹-C(O)R² or O=CR¹R² linkers.

Entry	Polymeric precursor	Released functionality	Ref.
1			[66a-c]
2			[61c,d;67a-e]
3			[68a-e]
4			[69]
5			[70a-c]
6			[71]

The use of a semicarbazone linkage as an anchor and reversible protecting group is depicted in entry 1 of Table 12.^[66a] The product ketone is resistant to both mildly basic and anhydrous acidic conditions, and can be released with aqueous HCl (PACT O=CRR). Ketones immobilized through an imine^[66b] or hydrazine^[66c] can be similarly released.

Substrates bound to the resin by means of an ester or amide tether have been liberated as ketones by the addition of a carbon nucleophile (Table 12, entry 2; PACT R¹–C(O)R²). The Weinreb amide linker, described earlier for the synthesis of aldehydes, undergoes cleavage in this way with Grignard reagents.^[61c,d]

The base-induced carbon nucleophile inherent to the Dieckmann condensation has also been exploited.^[67a–e] The ketone products revealed on cleavage and cyclization from the resin contain a β -keto or ester group and hence exist as their enol tautomers. Scheme 25 illustrates one of several

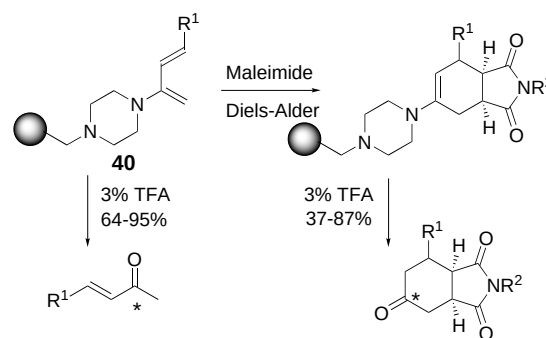


Scheme 25. PACT R(OC)C=CROH linker. Synthesis of tetramic acids where Dieckmann cyclization effects cleavage and cyclization and subsequent enol formation.^[67b]

solid-phase syntheses of tetramic acids.^[67b] Wang resin bound amino acids underwent acylation with an acetic acid derivative after deprotection of the 9-fluorenylmethoxycarbonyl (Fmoc) group and reductive alkylation with an aldehyde to give **38**. Cleavage and cyclization proceeded using tetrabutylammonium hydroxide as the base, which is effectively scavenged after the reaction with acid Amberlyst A-15 resin to deliver the products **39** in excellent yield (PACT R(OC)C=CROH).

An enamine linkage, represented schematically in entry 3, of Table 12 has also been shown to release ketones on treatment with weak acid (Scheme 26). In the preparation of resin-bound 2-aminobutadienes as substrates for [4+2] cycloadditions, a piperazine tether is used to immobilize propargylphosphonium bromide, which is converted into **40** after a Wittig reaction. Direct cleavage with TFA gives enones,^[68a] and the enamine resulting from a Diels–Alder reaction affords saturated cyclic ketones with a PACT O=C(R)CR₂H vestige.^[68b]

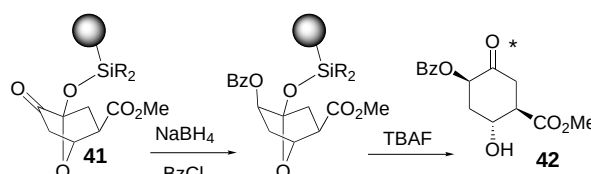
Processes employing a resin-bound enol ether^[68c] and a silyloxydiene tether^[68d] have been shown to react in the same way. The acid labile ketone linker shown in entry 4 of Table 12 has been used for the synthesis of a variety of 2-cyclohexenones.^[69]



Scheme 26. PACT O=C(R¹)CR₂H linker. 2-Aminobutadiene as Diels–Alder substrates, cleaved under mild acidic conditions.^[68a,b]

As for aldehydes, ketones can be immobilized by means of an acetal^[70a] or thioacetal tether^[70b,c] (Table 12, entry 5). The former, as before, is cleaved using acid while the sulfur analogues liberate the ketone products on oxidative desulfurization with [bis(trifluoroacetoxy)iodo]benzene or anhydrous periodic acid.

Scheme 27 shows an example reported by Schlessinger and Bergstrom of the general, structurally more involved, linker summarized in entry 6 of Table 12. Immobilized substrate **41**,



Scheme 27. PACT O=C(R)CR₂CR₂C(R)OH linker. 4-Hydroxycyclohexanones released from a silyloxy tether by fluoride.^[71]

constructed by means of the Diels–Alder reaction of a resin-bound furan, undergoes stereoselective reduction prior to fluoride cleavage.^[71] For this specific example, the 4-hydroxy substituent of cyclohexanone **42** is also created during this cleavage and the linker can be named accordingly as PACT O=C(R)CR₂CR₂C(R)OH. This is an example of how the length of the “PACT” term may often prove to be proportional to the generality of the linker.

11. Formation of Alcohols and Thiols

PACT H–OR, PACT H–SR, and PACT HO–R Linkers

Some of the first new linking technologies to depart from the formation of carboxylic acid derivatives were those designed for the immobilization and release of alcohols. An expansive array of linkers with this capacity have now been developed (Table 13).

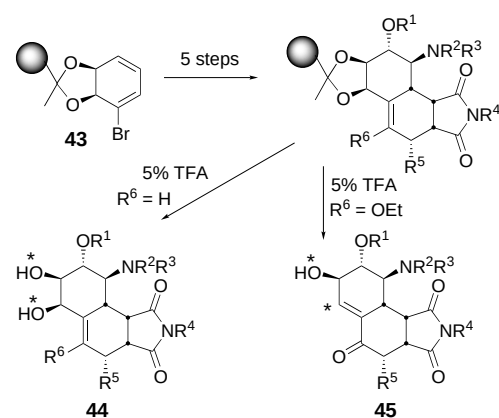
Ellman and co-workers' linker based on the tetrahydropyranyl (THP) protecting group is analogous to a simple resin-bound vinyl ether proposed by Wang and is cleaved under the usual acidic conditions, (Table 13, entry 1; PACT H–OR).^[72a–e] Leznoff and co-workers have made use of the acid-labile trityl protecting group in the synthesis of

Table 13. Alcohol and thiol formation: PACT H-OR, H-SR, and HO-R linkers.

Entry	Polymeric precursor	Released functionality	Ref.
1		H-OR	[72a–c]
2		H-OR	[73a–g]
3		HO-OR	[74a–c]
4		HO-OR	[75a,b]
5		H-OR	[77a–f]
6		H-OR	[79a–g]
7		H-OR	[80a–d]
8		H-OR	[44b,82a–h]
9		H-SR	[83a,b]

various insect pheromones on the solid phase (Table 13, entry 2).^[73a,b,d,e]

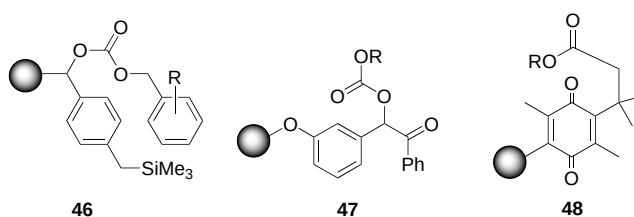
Table 13, entry 3, outlines the use of the acetal tether for the immobilization and release of 1,2-diols or catechols.^[74a–c] Employing such a system, Wendeborn et al. has elaborated a resin-bound cyclohexadienediol substrate **43** (Scheme 28)^[74a] by means of epoxidation, nucleophilic ring-opening, Pd⁰ cross-coupling, and Diels–Alder reactions. The highly functionalized products were cleaved from the resin under acidic conditions: depending on the substitution pattern, diols **44** (PACT H-OCR₂CR₂O-H vestige) or γ -hydroxy- α,β -enones **45** (PACT H-OCR₂CH=CRC(O)R vestige) were released.



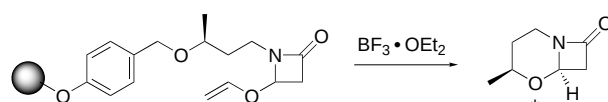
Scheme 28. PACT H-OCR₂CR₂O-H and PACT H-OCR₂CH=CRC(O)R linker. Immobilization of cyclohexadiene diols onto a ketal tether and their release as 1,2-diols or γ -hydroxyenones.^[74a]

Oxidative cleavage of resin-bound aryl boronic acids with hydrogen peroxide in the presence of sodium hydroxide has been shown to liberate phenols in high yield (Table 13, entry 4).^[75a,b] Transesterification or acid hydrolysis will release a boronic ester^[75a] or acid.^[75b] This linker involves a resin-bound diol: reversal of the tether such that the boronic ester is resin-bound allows for the release of diols;^[76a–c] this system has been applied to the selective blocking of *cis*-hydroxyl groups of carbohydrates.

The trialkylsilyl,^[73g, 77a–c] dialkylarylsilyl^[77e] or dialkoxysilyl^[77f] linkers depicted in entry 5 of Table 13 have been used with success for the release of alcohols by fluoridolysis. These release conditions have also been employed in the formation of benzylic alcohols from the more complex silyl-activated linker **46**.^[78]



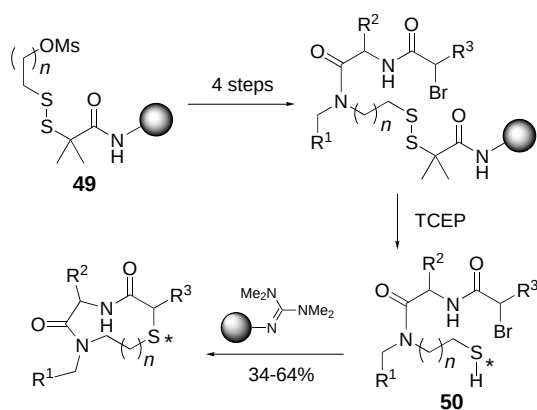
Both phenolic and alcoholic products are accessible using the *p*-alkoxybenzyl tether in entry 6 of Table 13. The benzylic ether bond is typically cleaved with TFA,^[79a–d] but 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has the same effect.^[79e] An interesting application of such a linker, the synthesis of 1-oxacephams, has been reported by Chmielewski and co-workers (Scheme 29).^[79f,g] The Lewis acid induced loss of the vinyloxy substituent followed by trapping of the resulting carbocation by the benzylic oxygen atom results in cleavage and cyclization.



Scheme 29. PACT H-OR linker. 1-Oxacepham synthesis by nucleophilic displacement at the C4 position of the azetidine-2-one ring.^[79f,g]

Alcohols or phenols bound to the solid phase by means of a simple ester linkage (Table 13, entry 7) are cleavable by basic hydrolysis.^[80a,b] Many interesting variants have been synthesized: **47** is photolabile^[80c] and an alternative to the *o*-nitrobenzyl linker,^[46a, 81a,b] whereas **48**, with the redox-sensitive *p*-benzoquinone core, cyclizes to expel the product on reduction with sodium hydrosulfite to the hydroquinone.^[80d] The formation of primary alcohols by reductive cleavage of esters,^[44b, 82a,b,h] thioesters,^[82c–f] or amides^[82g] with diisobutylaluminum hydride (DIBAL-H), LiAlH₄, or LiBH₄ has also been exploited (Table 13, entry 8).

An interesting linker with the capacity to release thiols has been reported by Ellman and co-workers (Table 13; entry 9).^[83] In a synthesis of β -turn mimetics (Scheme 30), the resin-bound mesylate **49** undergoes amine substitution, amino



Scheme 30. PACT H-SR linker. Synthesis of putative β -turn mimetics. Disulfide cleavage with TCEP precedes an intramolecular S_N2 reaction that is catalyzed by a resin-bound guanidine base.^[83a,b]

acid coupling, and acylation to incorporate three degrees of diversity. The acyclic mimetic **50** is liberated by disulfide cleavage with tris-(2-carboxyethyl)phosphane (TCEP) and cyclization is induced by a resin-bound guanidine base which serves also to scavenge excess reagent and by-products. Significantly, potent ligands to somatostatin receptors have been identified following the screening of a mimetic library prepared with this technology.^[83b]

12. Summary and Outlook

In the past decades, few areas of chemistry have enjoyed such an explosion of interest as solid-phase chemistry. Although conceived for peptide synthesis, gone are the days when the technology was applied solely to this end; the repertoire of organic reactions developed on the solid phase is considerable and approaching that used in conventional solution-phase chemistry.

Concurrent with and complementary to the diverging of this field, we have witnessed the rapid growth of novel linking technologies and there now exist means for the incorporation of most fundamental functional groups at the former linkage site of a product liberated from its support.

While some of these are very general and could, in theory, be applied to the release of a myriad of product classes, such as the PACT alkyl or PACT aryl linkers, others are arguably less so and are cleaved to release rather more specific functionalities. All have their value, however, in view of the requirement for cleavage conditions that are both compatible with a product's integrity and applicable to robotic techniques.

Concerned, as it is, only with the functionalities released on cleavage, the classification suggested in this article allows for a universal linker nomenclature which avoids the necessity for ambiguous terms such as "traceless". It is anticipated that such a classification will also facilitate the choice of a linker in regard to a given target for solid-phase synthesis.

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Protean

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Science often advances upon willful transgression of a seeming interdiction. Examples which leap to a chemist's mind are noble gas compounds, strained hydrocarbons such as tetrahedranes, activation (by organometallics) of even methane, and, to mention just one brilliant, more recent achievement, inclusion of an allene within the confines of a six-membered ring while preventing its conversion into a benzenoid.^[1] Such feats require all the cunning of a scientist in coaxing and, yes, coercing the system at hand to obey instructions from a daring imagination.

As always, it is hard. Not for nothing is our playroom called a *laboratory* (*labor*, from Latin, to work or to suffer). And when the task is done and the time arrives to convey to others (who might not be privy to the anguish of the work) all that struggle and the majesty of the achievement, the scientist quite naturally lapses into metaphor. One such metaphor, founded in male 19th century language as much as in history, is "Unveiling the Secrets of Nature",^[2] which may appear as some more or less prurient variant. Another example, evoking the thorny, twisted path to understanding and the long hours of toil in the laboratory, is "Wrestling with Nature."

The latter metaphor has been central to experimental science since at least the Elizabethan Age, and is the subject of this small essay. While the roots of the metaphor lie in Greek myth, it makes a striking debut in science in a seminal brief for experiments. This arresting phrase also marks a bifurcation in the way science is viewed by nonscientists, even—and especially so—in our day.

The textual proof here is that of Francis Bacon (1561–1626), in his book *Of the Advancement of Learning* from 1605. Bacon writes:^[3]

"For like a man's disposition is never well known till he be crossed, nor Proteus ever changed shapes till he was straitened and held fast; so the passages and variations of nature cannot appear so fully in the liberty of nature, as in the trials and vexations of art."

He repeats the imagery in his remarkable work of 1620 *Novum Organum*, which was a clarion call to replace what passed as Aristotelian reasoning about the world^[4] by experiment. Francis Bacon likens matter to Proteus, the "Old Man of the Sea", and describes scientific endeavor, as it strives to discipline matter, as follows:^[5]

"And the manipulations of art are like the bonds and shackles of Proteus, which reveal the ultimate strivings and struggles of matter."

By "art" Bacon clearly means experiment, as this passage makes clear:^[6]

"...every interpretation of nature which has a chance to be true is achieved by instances, and suitable and relevant experiments, in which sense only gives a judgment on the experiment, while the experiment gives a judgment on nature and the thing itself."

Three hundred and sixty-five years later, Primo Levi, in his wonderful chapter on hydrogen in the book *The Periodic Table*, writes:^[7]

"We would be chemists, Enrico and I. We would dredge the bowels of mystery with our strength, our talent: we would grab Proteus by the throat, cut short his inconclusive metamorphoses from Plato to Augustine, from Augustine to Thomas, from Thomas to Hegel, from Hegel to Croce. We would force him to speak."

What is going on here, and who is Proteus? Here is a pithy description:^[8]

"Proteus is a prophetic sea divinity, son of either Poseidon or Oceanus. He usually stays on the Island of Pharos, near Egypt, where he herds the seals of Poseidon. He will foretell the future to those who can seize him, but when caught he assumes all possible varying forms to avoid prophesying. When held fast despite his struggles, he will assume his usual form of an old man and tell the future."

The episode of Menelaos wrestling with Proteus in the *Odyssey* is one of the topoi of literature. The old man from the sea, when the hero and his companions try to catch him in their arms, first becomes a bearded lion (Figure 1), followed by—the sequence of creatures the magician turns himself into is not unlike the list of the years in the Chinese calendar!—a snake, a leopard, a huge boar, flowing water, and a high and leafy tree. But Proteus has to submit to the brute force of

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Figure 1. The struggle between Proteus and Menelaos as drawn by Patten Wilson.^[9]

Menelaos and his companions; firmly held, he finally consents to act as a seer—with the uncanny ability of a poet, that is, the ability to describe in vivid and memorable words the images which flock into the mind.^[10] Indeed, Proteus is an inspired speaker: when Socrates teases Euthyphro during their dialogue, he tells him that “like Proteus, you must be held until you speak”!^[11]

But how did we get from a wrestling match with Proteus (definitely male) to one with nature (mostly feminine in European culture)? Might there be an element of covering up anything remotely homoerotic as one moves on the trajectory out of the Renaissance and toward Victorian times? Is it just an erosion of classical culture as science leads the democratization of the professions? Bacon also resorts to the other metaphor:^[12] “...nature reveals herself more through the harassment of art than in her own proper freedom.” Whatever the reasons, by our own time, excepting stylists such as Primo Levi, Proteus is left in peace in his cave, and nature alone is cross-examined.^[13]

Francis Bacon, as an Elizabethan mind, was a master at crafting metaphors—think of his “idols of the tribe, idols of

the marketplace”.^[14] He also compared experimental scientists, good at collecting data, with ants; while theorists, he said, are more akin to spiders, “who make cobwebs of their own substance.” Not everyone was happy with the Lord Chancellor. One of our icons, Justus von Liebig, had this to say:^[15]

“Bacon attaches a great deal of value to experiments in research. But he understands their meaning not at all. An experiment not preceded by theory, i.e. by an idea, bears the same relation to scientific research as the sound of a child’s rattle does to music.”

Back to chemistry: we are indeed familiar with the real world being unruly, unyielding to our efforts to make it behave, and apparently uncontrollable. Quite a few chemical reactions (“metamorphoses” as they were termed in former times) seem to us like Proteus in their changes, whether they are predictable or not. Cascade reactions, which one of us was perhaps instrumental in naming,^[16] come to mind. We also know quite a few tricks to stop the old man of the sea in his tracks, when he comes to haunt chemical dynamics. The trapping of reaction intermediates is just such a tactic. So, to return to cyclohexa[1,2,4]triene—evidence for the fleeting existence of the parent hydrocarbon came from such trapping.^[17] Use of radical traps to expose certain chemical species (or to divert them from their appointed rounds) is a common trick.

Turning from reactivity to structure, there also we find an uncanny ability of matter to masquerade in an unpredictable diversity of shapes. Jack Dunitz and Joel Bernstein have written a wonderful account of vanishing polymorphs, crystal forms which were once synthesized, but then could not be recreated. Or so it seemed.^[18] Seed crystals have mysterious ways of propagating. The phenomenon is of great importance in the pharmaceutical industry, with respect to the differing efficacies of polymorphs, control of their production, and their patentability. Polymorphs belong to the realm of “the same and not the same”.^[19]

The “Wrestling with Nature” metaphor brought about a debate that roils the waters of Proteus’ father to this day. Bacon was accused of being the first of a long series of villains to “put nature on the rack”, a rationalizer of torture in the service of science.^[20] Goethe’s revulsion at Newton’s incarceration of a passage of light through a slit (and its subsequent analysis into the component colors by a prism) is emblematic. As are Donne, Wordsworth, and Ruskin’s impassioned denouncements of science and of the attendant industrial revolution. The line continues, to some (but hardly all) of the environmentalist and animal rights critiques of the interventionist nature of science.

This is not the place to enter into this debate. Our opinion is that modern commerce and technology, with the collusion of science, has some things to be ashamed of, such as the use of

animals in the devising of new cosmetics. And much more to be proud of, our truly democratizing science.

As a community, we have become aware that voyeurism of nature is neither innocent nor totally unobtrusive. We now know that it brings about its own retribution, perhaps like Acteon, who is direly punished for having watched Artemis in the nude. Werner Heisenberg has taught us that any measurement interferes, however slightly, with the system being studied. Is this a limitation to our knowledge? Yes, and no. To be sure, it encourages a more courteous approach to reality, forcing us to question macroworld intuition thoughtlessly applied to the microworld, forcing us to be delicate (as we should have been from the beginning) in asking our questions of nature. Take modern chemical dynamics, that remarkable crossroads of classical and quantal. The indeterminacy principle (for that is closer to what Heisenberg called it) has nontrivial consequences in the new kinetic art. It makes us think: To build and shape a femtosecond pulse, what range of energies does it take? And if we want to inject a precise dollop of energy into a bond, what does that entail for the time scale of the process?^[21]

Is intervention an absolute correlate of experimental science? The question merits a lengthier discussion. Surprisingly (given Bacon's startling metaphors and the resistance to them), it is only recently that philosophers have begun to explore the subject. An examination of the question is found in Ian Hacking's idiosyncratic work *Representing and Intervening*.^[22] In an important essay on "Experimentation and Scientific Realism", Hacking writes: "Interference and interaction are the stuff of reality."^[23] J. E. Tiles, in the essay "Experiment as Intervention" says of Hacking's analysis that it was "received in some quarters with a mixture of incomprehension and hostility."^[24] This is a minor surprise to us. We agree with Tiles that philosophers of science ought to consider that experiment does not only follow from observation (as classical empiricists mistakenly and narrowly assume; this is valid for Liebig as well). At times, experiment is driven by an overtly interventionist stance.

"Nature's narrative of herself" is a fiction. Any acquisition of knowledge involves intrusion. Only the size of the perturbation changes. Accordingly, we have learned to care. We do not want our curiosity to devastate its object, butterfly-like in its fragility. Instead of roughhouse "wrestling with nature," regardless of the consequences, we have made ourselves adept at gentler sports. Examples are various "noninvasive" spectroscopic techniques, for instance, spin tickling in nuclear magnetic resonance spectroscopy, or resorting to isotopes in order to effect as gentle a perturbation as we know how.^[25] And, of course, we can use all the fine information isotope effects give us....

We try to make our intrusions as delicate as a caress or a kiss. Though, God knows, some kisses can upset a world.

And, yes, we are part of nature too. When trying to understand a complex system or phenomenon—electrocyclic reactions, say, before they were understood—one's mind and one's art seem too limited. We cope with a complex skein of imprecise facts. We wrestle with how to explain phenomena.

Lack of sleep from contending with the truth of the matter is reminiscent of another wrestling match on the world's

spiritual stage. It is the story of Jacob wrestling with someone throughout the night. Here is how it is told in Genesis, chapter 32:^[26]

"Jacob was left alone. And a man wrestled with him until the break of dawn. When he saw he had not prevailed against him, he wrenched Jacob's hip at its socket, so that the socket of the hip was strained as he wrestled with him. Then he said, 'Let me go, for dawn is breaking.' But he answered, 'I will not let you go, unless you bless me.' Said the other, 'What is your name?' He replied, 'Jacob.' Said he, 'Your name shall no longer be Jacob, but Israel, for you have striven with beings divine and human, and have prevailed.' Jacob asked, 'Pray tell me your name.' But he said, 'You must not ask my name!'"

As we begin to see things for what they are in this world of chemistry, we are overwhelmed with the feeling of having striven with concepts both divine and human.

Proteus in time became an adjective. To be protean is to be variable in form, to take on or exist in various shapes. Was there ever a science that was more about change than chemistry? And is not the richness of our enterprise, the multitude of molecules we can make, the necessary complexity of the living state due to isomerism, so many chemical incarnations of Proteus? The adjective that serves as the title of this essay is an apt descriptor for chemistry itself.

- [1] M. A. Hofmann, U. Bergsträsser, G. J. Reiss, L. Nyulász, M. Regitz, *Angew. Chem.* **2000**, *112*, 1318–1320; *Angew. Chem. Int. Ed.* **2000**, *39*, 1261–1263.
- [2] For a lovely example, see the poem by one of our heroes, Humphry Davy, cited by D. Knight, H. Davy, *Humphry Davy: Science and Power*, Blackwell, London, **1993**. The metaphor presumes the enterprise of science is discovery. But chemists especially know that our business is, in substantial part, creation; see Chapter 19 in ref. [19].
- [3] See the version edited by G. W. Kitchin: F. Bacon, *Of the Advancement of Learning*, J. M. Dent, London, **1915**, p. 73.
- [4] We put it this way out of respect for Aristotle. Bacon and his era reacted against the scholastics, who "merely polished the idol of Aristotle's investigations—thousands of years after his time." Aristotle was (occasionally) a close observer of nature, as his *Historia Animalium* shows; his was "the boldest scientific thinking of his day." The Baconesque quotations here are from Michael Weisberg, Stanford University, private communication.
- [5] See the version edited by L. Jardine and M. Silverthorne: F. Bacon, *The New Organon, Book I*, Cambridge University Press, Cambridge, **2000**, p. 227.
- [6] See the version edited by L. Jardine and M. Silverthorne: F. Bacon, *The New Organon, Book I*, Cambridge University Press, Cambridge, **2000**, p. 45.
- [7] P. Levi, *The Periodic Table* (Translated by: R. Rosenthal), Schocken Books, New York, **1984**, p. 23.
- [8] www.pantheon.org/mythica/areas/greek; Copyright: **1999** Encyclopedia Mythica. All rights reserved. Protected by the copyright laws of the United States and International treaties.
- [9] An illustration from: Homer, *Odyssey* (Translated by: H. B. Cotterill), George G. Harrap, London, **1911**.
- [10] Homer, *Odyssey, book 4* (See, for example, the version in ref. [9], pp. 398–460).
- [11] Quoted from: Plato in *Plato in Twelve Volumes, Vol. 1, Euthyphro, 15d* (Translated by H. N. Fowler), Harvard, Cambridge, **1966**, p. 15.

- [12] See the version edited by L. Jardine and M. Silverthorne: F. Bacon, *The New Organon, Book I*, Cambridge University Press, Cambridge, **2000**, p. 21.
- [13] There is a related, but we think, different metaphor that has been loose in the philosophical literature. This is “carving nature at its joints”, brought to our attention by Michael Weisberg. It goes back to Plato’s *Phaedrus* (265e), and we think it refers to scientists (or philosophers) getting classifications or categories “right”.
- [14] For a reminder of the lasting validity of Bacon’s metaphor, see: S. J. Gould, *Science*, **2000**, 287, 253–261.
- [15] Liebig has much more to say, mostly uncomplimentary, about Bacon. He devotes one lecture and two long polemical essays (published in the *Augsburger Allgemeine Zeitung* in 1863 and 1864) to the other baron: J. von Liebig, *Reden und Abhandlungen*, C. F. Winter, Leipzig, **1874**, pp. 220–295. See also a discussion of Liebig’s essay in: G. Bachelard, *La formation de l’esprit scientifique*, J. Vrin, Paris, **1969**, p. 58–59.
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Plastic Transistors Reach Maturity for Mass Applications in Microelectronics**

Frank Würthner*

During the last decade of the twentieth century we witnessed a tremendous development in the field of organic materials for electronic devices. These practical applications were already initiated in 1977 by the revolutionary discovery of electrical conductivity in a polymer, polyacetylene, by Alan J. Heeger, Alan G. MacDiarmid, and Hideki Shirakawa who were awarded the Nobel prize for Chemistry in 2000.^[1] However, the first technical applications of (semi)conducting organic materials were not realized as synthetic metals but as photoconductors in copiers and laser printers,^[2] as light-emitting diodes (LEDs),^[3] and as antistatic coatings.

For these applications it was of considerable importance that apart from optimized molecular properties (redox potentials, stability of radical cations, luminescence) amorphous solid-state materials could be derived which allow a hopping transport of the charges from one interface to the other without being hindered by grain boundaries such as occurs in polycrystalline materials. On the other hand, as a result of the high structural and energetic disorder only low charge-carrier mobilities are possible in these amorphous solid-state materials, which accordingly can not compete with inorganic semiconductors in terms of the switching frequencies demanded in semiconductor electronics.

An increase in the charge-carrier mobility by several orders of magnitude is feasible in more ordered organic materials if the π systems exhibit sufficient π overlap with adjacent molecules in the crystal lattice and if macroscopic ordering on a suitable substrate leads to a desired orientation and large domain sizes. Another important aspect for a successful implementation of organic semiconductors in microelectronic switching and memory devices is the availability of p-type (=hole-carrying) as well as n-type (=electron-carrying) semiconducting materials to enable important logic elements such as pn junction diodes, bipolar transistors, and comple-

mentary circuits to be prepared. After a short overview of the progress achieved in the development of transistors based on p-type semiconducting organic materials during the 1990s the recent breakthrough in n-semiconducting organic materials will be highlighted in this article.

Figure 1 shows the basic scheme of a field-effect transistor (FET) which contains a thin active layer of a semiconductive organic material. The latter may be prepared by vacuum

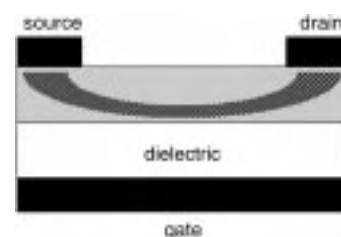


Figure 1. Schematic representation of an organic thin-film transistor (TFT) consisting of metallic contacts (black), a semiconducting organic layer (gray), and an insulating dielectric (white). After a voltage is applied at the gate electrode charges are injected into the semiconductor and a conductive channel (hatched in black) is generated between the source and drain electrodes. The charge carriers in these organic semiconductors are radical anions (n-type semiconductors) or radical cations (p-type semiconductors).

deposition or, at lower costs, by liquid phase processing techniques. When a voltage is applied between the source and gate electrode charge carriers are injected into the semiconductor (positive charge carriers in p- and negative charge carriers in n-semiconductors) which leads to the formation of a conductive channel. It is important for the performance of the transistor that upon application of the gate bias a substantial increase in the conductivity from an initially nonconductive state into a highly conductive state takes place (on/off current ratio $> 10^5$). After generation of the charge carriers at the insulator/semiconductor interface a current may flow from the source to the drain electrode, with the magnitude of the current being now mainly dependent on the source-drain voltage as well as the charge-carrier mobility.

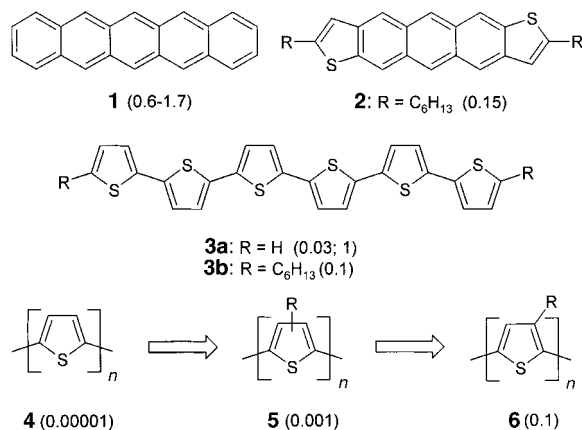
The only difference between these organic FETs and similarly constructed, commercially available TFT transistors^[4] is the active layer, which contains an organic semiconductor instead of amorphous silicon. However, all-plastic chips based entirely on organic materials have already been

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[**] I wish to thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for a Liebig and a Habilitanden fellowship, and Prof. Peter Bäuerle for numerous helpful discussions especially about the topic reviewed in this article.

demonstrated whose mechanical flexibility offers totally new perspectives to the rapidly growing market of identification and product tagging as well as for pixel drivers for flexible displays.^[5, 6]

Currently, the most developed organic FETs are based on pentacene **1**^[7] and oligo- or polythiophene **3–6** p-type semiconductors (Scheme 1).^[8, 9] The highest charge-carrier mobilities (up to $1\text{--}2\text{ cm}^2\text{ V}^{-1}\text{ s}^{-1}$) and the highest on/off ratios



Scheme 1. Examples of p-type organic semiconductors with high field-effect mobilities (numbers in parentheses are in $\text{cm}^2\text{ V}^{-1}\text{ s}^{-1}$ for thin-film transistor devices; only the second value for **3a** was measured from a single crystal).

(more than 10^6) are realized by vacuum deposition of the low molar mass derivatives. Although these values are not in the range demanded for high-performance applications such as computer chips, they match the requirements for numerous other application such as pixel drivers for liquid crystal displays or basic switching and memory chips. It is known from X-ray diffraction data that these materials exhibit a crystalline ordering (in contrast to the above-mentioned amorphous semiconductors in xerography and in LEDs^[2, 3]) which is essential for the high conductivity in the channel between the source and drain electrode.^[8]

Interestingly also, (undoped)^[10] polymeric materials with continuously increasing mobility have been prepared during the last few years despite the fact that they are more disordered and deposition from solution has to be carried out under less stringent conditions. In the case of polythiophenes an increase in the mobility from 10^{-5} (in 1986) up to $0.1\text{ cm}^2\text{ V}^{-1}\text{ s}^{-1}$ (in 1998)^[9] could be achieved by first improving the solubility (and the related processability) of the polymer by means of β -alkyl substituents (**5**) and finally increasing the supramolecular order by a regioregular attachment of these substituents at the polythiophene backbone (**6**).^[8, 9] As a result of the regioregularity of these β -alkyl substituents highly ordered microcrystalline domains are formed which lead to a favorable merger of polymer-type properties (such as processability) with structural ordering, as is typically observed in liquid crystalline (microphase segregation) and crystalline materials (interdigitation of alkyl chains).^[11]

In contrast to organic p-type semiconductors, n-type semiconductors remained less developed for a long time. This was partly a result of the lack of electron-poor polymers but also because of theoretical arguments which predict a reduced

stability of the n-conducting radical anions under ambient conditions.^[12] This situation is illustrated in Figure 2 for a number of typical electron-poor π systems which all exhibit

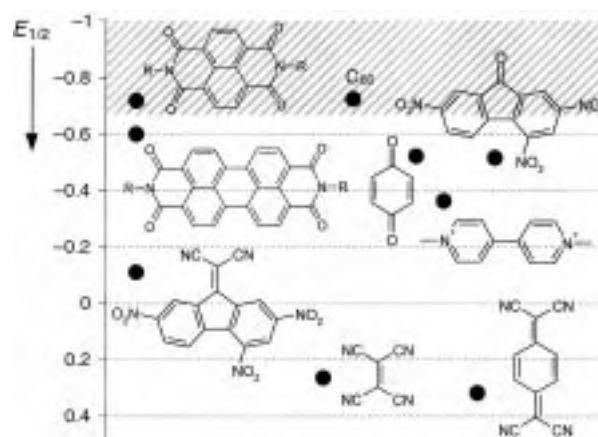
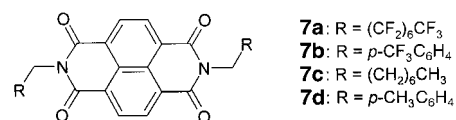


Figure 2. Reduction potentials $E_{1/2}$ in V (versus the standard calomel electrode) of potential n-type semiconductors according to cyclic voltammetric measurements made in solution. From the thermodynamic point of view none of these redox couples are sufficiently high to arrive at n-type doped materials which are stable under ambient conditions (oxygen reduction $\text{O}_2 + 4\text{H}^+ + 4\text{e}^- \rightarrow 2\text{H}_2\text{O}$ at $E_{1/2} = +0.57\text{ V}$; water reduction $2\text{H}_2\text{O} + 2\text{e}^- \rightarrow \text{H}_2 + 2\text{OH}^-$ at $E_{1/2} = -0.66\text{ V}$ (hatched area)).^[12]

reduction potentials below the half-wave potential of oxygen.^[13] Therefore, from the thermodynamic point of view, vacuum conditions or encapsulated devices should be mandatory in the case of n-channel FETs.

Against this background the recent work of Katz and co-workers was very surprising. They reported high electron mobilities ($>0.1\text{ cm}^2\text{ V}^{-1}\text{ s}^{-1}$) and excellent on/off current ratios ($>10^5$) for the fluorine-substituted naphthalenebisimides **7a, b**, even in the presence of air.^[14] These remarkable



results can be explained by the following:^[14a] 1) Naphthalene-bisimide radical anions are generated by the gate bias. 2) There is a favorable macroscopic ordering of the naphthalenebisimide molecules at the semiconductor/insulator interface which allows for high lateral charge carrier mobilities (see Figure 1). 3) The remarkable stability of these transistors in air is the result of a dense packing of the fluorinated chains which prevents the penetration of oxygen and water into the n-conducting channel region. Comparative studies on *N,N'*-dialkyl- and -dibenzyl-naphthalenebisimides **7c, d** did not show this quality, despite an even higher mobility of **7c** under ultra-high vacuum conditions (up to $0.16\text{ cm}^2\text{ V}^{-1}\text{ s}^{-1}$).

In the meantime two more papers appeared on the electrochemical and crystallographic studies of these compounds and confirmed these initial statements. All the naphthalenebisimides studied exhibit reversible reduction

waves in their cyclic voltammograms, with the highest value being for **7a** with a potential of about -0.6 V (versus SCE).^[14b] The solid-state single-crystal X-ray crystallographic study on all the investigated compounds (**7a–c**)^[14c] revealed layer structures which seem suited for charge transport within two dimensions (herringbone packing motif, similar to oligothiophenes^[8]). These layers, especially in the case of **7a**, are separated by densely packed fluorinated chains that provide a barrier against the diffusion of oxygen into the n-type channel. Additional conductivity measurements as a function of temperature carried out on single crystals of **7c**, **d** suggest that a bandlike charge-transport mechanism occurs at temperatures < 300 K.^[14c]

In addition to these naphthalenebisimides, experiments performed on perfluorinated copper phthalocyanines,^[15] perylenebisimides,^[16] and α,α' -diperfluorohexyl-substituted sexithiophene^[17] recently revealed impressive n-type mobilities. These results show there is now a higher variety of n- than p-type low molar mass materials. Moreover Schön et al. succeeded in the preparation of ambipolar FETs based on single crystals of pentacene (**1**)^[18a] and sexithiophene (**3a**)^[18b] which showed p- as well as n-type semiconductivity depending on the gate bias. After this encouraging progress it seems to be only a question of time until n-type semiconducting polymers and mass-produced chips are available which make use of the cost and processing advantages of organic compared to inorganic materials.

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Labeling of Biomolecules for Medicinal Applications—Bioorganometallic Chemistry at Its Best**

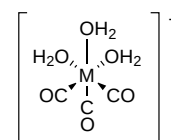
Nils Metzler-Nolte*

The modification of proteins with transition metal compounds has furnished valuable insights into the structure and function of biomolecules. In addition to fundamental aspects, these insights have an impact on medicinal research and applications. In the majority of investigations, transition metals in Werner-type coordination complexes were employed with “hard” donor atoms such as N, O, or S of carboxylates, alcoholates, amides, amines, and sulfides. Other properties, and consequently different reactivity, towards biomolecules is expected from transition metals in organometallic compounds. These are typically stabilized by π back-bonding ligands such as CO, phosphanes, or aromatic π systems, for example η^6 -arenes or η^5 -cyclopentadiene (Cp). Contrary to common belief among chemists, these compounds may indeed exhibit remarkable stability in aerobic, aqueous media—given a judicious choice of metal and ligands. In addition, the special chemical or spectroscopic properties of organometallic complexes may be used advantageously for the site-selective reaction with biomolecules or the direct detection of the new bioorganometallic compound. In this rapidly growing area of interdisciplinary research, a number of groups have recently reported remarkable progress.

^{99m}Tc ($t_{1/2} = 6$ h) is a metastable isotope of the long-lived ^{99}Tc isotope ($t_{1/2} = 2.13 \times 10^5$ y). It is by far the most widely used isotope in radiopharmaceuticals.^[1–5] This preeminent position is due to its very favorable physical properties: A half-life of 6 h is long enough to carry out chemical synthesis and get useful images after administration to the patient. At the same time, it is short enough to permit administration of relatively high amounts of ^{99m}Tc radioactivity without exposing the patient to dangerous radiation doses. The 140 keV photons give excellent images; the ^{99m}Tc isotope is readily available from commercial ^{99}Mo – ^{99m}Tc generators. In these reactors, TcO_4^- is eluted from alumina-adsorbed [^{99}Mo]molybdate. Depending on factors such as generator age and prior elution times, the generator eluent contains between 20 and 85% ^{99m}Tc , with the long-lived ^{99}Tc being the only by-product and the total Tc concentration in the μM range. It follows from the radiophysical bounding conditions that any ^{99m}Tc radiopharmaceutical must be prepared and used “on the spot”. Preparation of the compound must be fast and ideally a “kit” formulation without the need for subsequent purification

should be provided for maximum ease and safety of use by technical staff in hospitals. Recently, Roe and co-workers presented a new preparation of high specific activity Tc complexes by solid-phase methods which does not require subsequent purification by HPLC.^[6] All the requirements are also met by new organometallic Tc complexes which are rapidly formed in high yield and purity when the generator eluent is directly added to a vial containing all reagents under a CO atmosphere.

Schubiger, Alberto, and co-workers reported the synthesis and applications of the astonishing complex *fac*- $[\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ (**1**).^[7] This simple complex combines a



- 1: M = Tc
2: M = Re

“lower” organometallic half with three carbonyl ligands with an “upper” Werner-type half with three water molecules as ligands. Like its Re analogue $[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ (**2**), **1** is stable for days in aqueous solution without decomposition. The interesting radioisotope ^{99m}Tc (see above) is readily available in hospitals from a ^{99}Mo reactor. From this device, a saline solution (0.9% NaCl in H_2O) of $[\text{O}_2\text{TcO}_4]^-$ is obtained with typical Tc concentrations around 1 μM . In their patented method, Schubiger’s group react this saline solution directly with excess NaBH_4 under 1 atm of CO and obtain **1** quantitatively in less than 20 min. The success of this reaction is all the more remarkable, because in the absence of CO only small amounts of TcO_2 are produced by NaBH_4 , and CO itself is only poorly soluble in water (approx. 1 mM at 25 °C). Taking the low concentration of TcO_4^- into account, a trimolecular reaction is highly unlikely for kinetic reasons alone. Other reductants such as SnCl_2 and $[\text{S}_2\text{O}_4]^{2-}$ do not give **1** or **2**, and it appears very likely that an intermediate is formed from BH_4^- and CO which effects the reduction reaction and stabilizes possible metal carbonyl intermediates en route to **1** or **2**, for example the well-known $\text{H}_3\text{B} \cdot \text{CO}$ adduct.

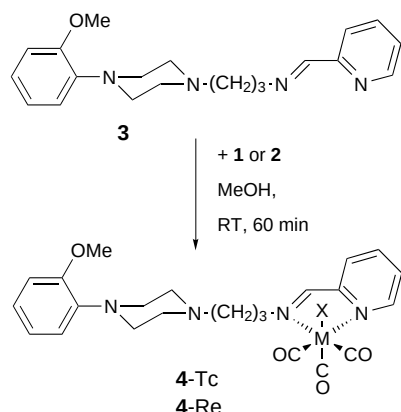
Water and CO ligand-exchange reactions on **1** were recently reported.^[8] The moderately fast exchange of ^{12}CO for ^{13}CO could be elegantly monitored by ^{99}Tc NMR spectroscopy through the subsequent appearance of a doublet, a triplet, and finally a quartet due to coupling to up to three ^{13}C nuclei, and an isotope shift $\Delta\delta = 1.05$ per carbon mass unit was determined. When **1** is left to stand under CO pressure for two weeks, all water molecules are slowly exchanged for CO, and the homoleptic $[\text{Tc}(\text{CO})_6]^+$ carbonyl complex is formed in equilibrium with partially carbonylated

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[**] The author thanks A. P. Schubiger and D. Grotjahn for reprints, and K. Severin for insightful discussions. The data in Figure 1 are used with the help and kind permission of M. Salmann and G. Jaouen. I am also grateful to Drs. H. & H. Weiss for their hospitality when writing this article.

species. $[\text{Tc}(\text{CO})_6]^+$ was prepared by Hieber and co-workers in 1965 but was characterized only by elemental analysis.^[9] As a result of the high symmetry of the cation, Merbach et al. obtained beautifully resolved NMR spectra and measured values of $\delta(^{99}\text{Tc}) = -1961$, $\delta(^{13}\text{C}) = 190.2$ and $^1J(\text{Tc}, \text{C}) = 261$ Hz for $[\text{Tc}(\text{CO})_6]^+$. In the logical next step, it was shown how **1** can actually be used for the labeling of biomolecules.^[10, 11]

The challenge for a new generation of radiopharmaceuticals is the selective targeting of specific receptors. As expected, the three water ligands of **1** are readily replaced by other donors, for example amines. In particular, aromatic amines such as histidine give very stable complexes. A pharmacologically interesting complex **4-Tc** was prepared with the Schiff base derivative of arylpiperazine **3** (Scheme 1).^[10] Arylpiperazines are the most thoroughly



Scheme 1. Labeling of arylpiperazine **3** as a serotonergic receptor ligand with **1** or **2**.

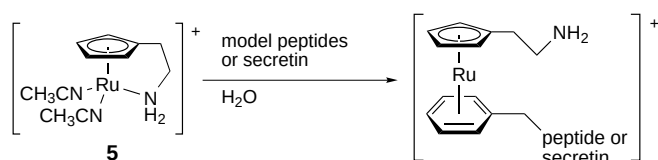
studied class of molecules for the 5-HT_{1A} subclass of serotonergic receptors in the central nervous system (CNS). Compared to the success in radiolabeling of other peptides and proteins, there are very few examples of $^{99\text{m}}\text{Tc}$ labeling of CNS receptor ligands. For **4-Tc**, a labeling yield of 90–95 % was achieved without subsequent purification, giving specific activities in the range of 30 GBq μmol^{-1} . This activity is about one order of magnitude better than can be achieved with more traditional Tc complexes with an 'N₂S₂' ligand set. Receptor affinity and selectivity of **4** were investigated by using the nonradioactive Re analogue **4-Re**. Conjugate **4-Re** shows high binding affinity to the 5-HT_{1A} receptor (5 ± 2 nM). Also, the selectivity of **4-Re** for its target receptor is high as shown by binding constants of $>1 \mu\text{M}$ for related receptors 5-HT_{2A}, dopamine-D2, 5-HT-transporter, and D-transporter. Finally, the stability of the bioconjugate under physiological conditions is excellent. Neither UV/Vis spectroscopy nor TLC analysis of the "cold" **4-Re** showed any decomposition of the complex after 24 h incubation in serum at 37 °C.

Another very attractive target for radiolabeling is presented by single-chain antibody fragments (scFvs), which have the potential for tumor imaging. They are easily produced in pure form from combinatorial libraries and cell expression, for example in *E. coli*. Compared to whole antibodies, scFvs are less prone to inactivation and degradation in the body. In addition, they penetrate cell membranes rapidly and yield

high tumor-to-background ratios. Unfortunately, there is no convenient method for $^{99\text{m}}\text{Tc}$ labeling of scFvs. Following expression in *E. coli*, scFvs are routinely purified by immobilized metal ion affinity chromatography (IMAC). To this end, a so-called His-tag, consisting of a number of histidine residues, is added to the N-terminus of the peptide. This His-tag provides an excellent chelating ligand for **1**, and indeed complexes of high stability were rapidly formed with a number of His-tagged scFvs.^[11] In an optimized protocol, a solution of **1** was mixed with the scFv solution and activities up to 3.3 GBq mg^{-1} (corresponding to 90 % labeling yield) were obtained. In a series of test experiments, the purity and identity of the $\text{Tc}(\text{CO})_3$ -labeled scFvs were established and the His-tag was confirmed to be the site of labeling by comparison with a His-tag-free scFv and monitoring the loss of radioactivity after incubation with a 100-fold excess of free histidine. In vivo stability studies were carried out with $^{99\text{m}}\text{Tc}(\text{CO})_3$ -labeled anti-mucin scFv M12 in mice. Gel filtration profiles of whole mouse serum analyzed 1 h after injection showed 75 % of the activity migrating with intact scFv and most of the remainder in the albumin fraction. In accordance with its small size, the labeled scFv is secreted through the kidney and all of the activity in urine is bound to the scFv fragment. Finally, biodistribution and tumor localization of $\text{Tc}(\text{CO})_3$ -labeled scFv M12 and anti-HER2 scFv 4D5 were indistinguishable from the respective ^{125}I -labeled scFv.

The favorable properties of **1** are mainly attributed to its unusual ligand set. The σ -bound water ligands in **1** are readily displaced by other ligands, but in combination with other push–pull ligands, the carbonyl groups impart a high kinetic stability on $\text{Tc}(\text{CO})_3^+$ derivatives like **4**. In addition, a high thermodynamic stability results from the d^6 low-spin electron configuration of the Tc^I complex. Although it was used in Tc-isocyanide compounds introduced by Davison and co-workers for heart imaging 15 years ago ("Tc-Sestamibi"),^[12] the oxidation state +1 is rather unusual in biologically active Tc compounds and difficult to stabilize with Werner-type ligands (typically with an N, O, or S donor set) alone. In this respect, organometallic complexes with CO ligands expand the available range of compounds significantly.

Complexes with η -bound π ligands, for example, $[(\eta\text{-C}_6\text{H}_6)\text{Cr}(\text{CO})_3]$ or $[(\eta\text{-C}_6\text{H}_6)\text{RuCp}]^+$, represent another typical class of organometallic compounds. Good stability of both types of compounds in aqueous solutions has been demonstrated and $[\text{CpRu}]^+$ –benzene derivatives are valuable starting materials for the synthesis of aryl ethers.^[13] Furthermore, the cationic $[\text{CpRu}]^+$ fragment readily coordinates to amino acid derivatives like amides and esters, and this behavior has been developed and patented by Beck and co-workers into a transition metal catalyzed solution-phase peptide synthesis scheme.^[14–16] Grotjahn et al. have now found an interesting temperature effect on the coordination mode of the donor-substituted $[\text{CpRu}]^+$ derivative **5** in a series of model compounds (Scheme 2).^[17, 18] Donor-substituted cyclopentadienyl complexes of early transition metals have recently received considerable attention as polymerization catalysts ("constrained geometry" catalysts). Upon addition of **5** to model peptides like Boc-Met-Phe-OMe or Boc-Phe-His-OMe



Scheme 2. Schematic representation of the reaction of **5** with aromatic rings in amino acids and peptides.

(Boc = *tert*-butoxycarbonyl, Met = methionine, Phe = phenylalanine) at room temperature, several species originating from σ bonding to the thioether or nitrogen donor groups are observed. After the sample had been heated to 60 °C for 6 h, the ^1H NMR spectra simplify considerably and only one species is observed with typical signals for π coordination of the $[\text{CpRu}]^+$ moiety to the phenyl ring (Scheme 2). This behavior was exploited by the authors for the selective labeling of secretin, a 27-amino-acid peptide with a molecular weight of about 3 kDa. Secretin is a gastrointestinal peptide hormone and has a unique phenylalanine residue at position 6 along with an N-terminal histidine, four arginine, one aspartate, and two glutamine residues, all of them providing good coordinating groups for transition metal fragments. When a solution of **5** is added to an aqueous solution of secretin in an NMR tube at room temperature, a relatively clean NMR spectrum is obtained after 8 h. Most significantly, the phenylalanine signals in the aromatic region are quantitatively shifted to higher field (ca. 6.2 ppm) which is diagnostic for coordination of arenes to the $[\text{CpRu}]^+$ moiety. Coordination of $[\text{CpRu}]^+$ to secretin is substantiated by electrospray ionization mass spectrometry. Finally, Edman degradation provides additional proof that the site of labeling is indeed the phenylalanine residue 6, since in the HPL chromatogram of partially degraded Ru-secretin the peak for phenylalanine is clearly missing. The site-selectivity of this reaction in the presence of over 25 concurring amide bonds, carboxylate groups, and even a histidine (remember the excellent binding of **1** to His described above!) is astonishing. Grotjahn and co-workers observed a “water-effect” in that the migration of the $[\text{CpRu}]^+$ fragment from N, S, O σ coordination to the π complex is considerably faster for secretin in water than for model peptides in water–methanol mixtures. Quite possibly, the relatively unpolar $[(\text{benzene})\text{RuCp}]^+$ fragment is thermodynamically stabilized in water compared to $[\text{CpRuL}_3]^+$ complexes, where L are hard donor ligands from the peptide (N, S, or O). This stabilization may manifest itself already in the transition states and serve to explain the observed kinetic effect. Alternatively, intermediates with coordinated water molecules (analogous to **1**) seem very likely and this issue will surely merit further investigation. As for **1**, the organometallic moiety $[\text{CpRu}]^+$ provides unrivaled selectivity and stability which is not readily achieved with traditional coordination complexes.

Significant progress is also reported in the application of bioorganometallic compounds for biological assays. It has been recognized for some time that IR spectroscopy of organometallic carbonyl groups provides a useful handle for the detection of organometallic bioconjugates even in a complex environment like cell extracts of the serum of

patients. This is attributed to the fact that the stretching vibrations of the terminal carbonyl group in organometallic complexes are observed at around 2000 cm^{-1} , a region where most organic molecules do not absorb. Moreover, these bands usually have high extinction coefficients and thus high sensitivity is obtained. The application of this technique to steroid hormones, peptides, and biogenic amines has been pioneered by Jaouen and his group and the technique has been dubbed carbonyl *metalloimmunoassay* (CMIA).^[19, 20] Application of this immunoassay obviates the need for radioactive markers, which constitutes the main advantage of this technique. For routine use in hospitals, the technique is in competition with other nonradioactive assays based on enzymatic methods or fluorescence, which work very reliably and in most cases easily achieve the required sensitivity and selectivity. However, none of these techniques is readily set up for simultaneous assaying of more than one analyte. On the other hand, there is considerable pressure on existing health care systems to save cost without compromising patient care. Analyzing for several species in one and the same assay seems like a promising approach to this end. Jaouen and co-workers at the Université Paris Sud have now published extensions of the CMIA technique for the simultaneous analysis of two^[21] and even three compounds in a special issue of the *Journal of Organometallic Chemistry* on bioorganometallic chemistry.^[22] Along with improvements in instrumental design,^[23] a simultaneous quantitative analysis of several species, for example monitoring the drug levels in blood, may now be carried out on as little as 20 μL of serum.

The method is based on the diversity of metal carbonyl stretching frequencies in various carbonyl complexes.^[22] Table 1 contains three examples of such complexes, **6–8**, together with their characteristic (analytical) stretching vibrations $\nu(\text{CO})$. By chemical synthesis, metal complexes were covalently linked to the three anti-epileptic drugs carbamazepine (CBZ), phenobarbital (PB), and diphenylhydantoin (DPH) to yield conjugates **6–8**. Mono-CMIAs have been established for these drugs before. A “cocktail” of all three is often prescribed by physicians to patients suffering from epilepsy. As for many drugs, individual patient response

Table 1. Organometallic carbonyl complexes of antiepileptic drugs and their IR carbonyl stretching frequencies. The characteristic band is printed in boldface.

Metal carbonyl complex	$\tilde{\nu}$ [cm^{-1}]
 6: R = Carbamazepine	2095, 2058 , 2032
 7: R = Phenobarbital	2033 , 1958
 8: R = Diphenylhydantoin	1973 , 1899

varies considerably and thus, a continuous monitoring of actual serum concentrations is mandatory at least in acute care in hospitals. This way, the optimum dose for each individual patient is secured and undesirable side effects are minimized.

For each of these drugs, polyclonal antibodies were obtained by established procedures from rabbits. In preliminary mono-CMIAs, it was confirmed that none of the antibodies showed cross-reactivity with the other two drugs nor with the other two tracers. Figure 1 shows the $\nu(\text{CO})$

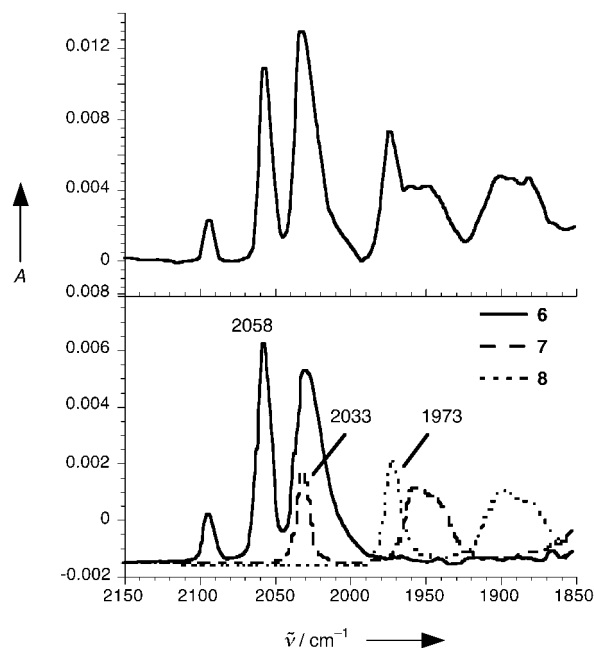


Figure 1. Carbonyl region of IR spectra of an equimolar mixture of **6**, **7**, and **8** (top) and of individual spectra of the three complexes (bottom). Characteristic bands for all three complexes are marked in the bottom spectra.

region of an IR spectrum of a mixture of **6–8**, along with a superimposition of IR spectra of the pure compounds at equal concentrations, which highlights the mathematical problem. The analytical band for complex **6** (at 2058 cm^{-1}) is free from interference with other bands and directly suited for quantitative analysis. In contrast, the analytical band for **7** (at 2033 cm^{-1}) is completely buried under the 2032 cm^{-1} band of **6**, and the analytical band of **8** (at 1973 cm^{-1}) partially overlaps the 1958 cm^{-1} band of **7**. Nevertheless, a quantitative deconvolution based on least-squares algorithms or a univariate method is possible and together with the known molar extinction coefficients of the three compounds yields minimum detectable quantities around 1 pmol . Validation of the multi-CMIA method was performed by comparison of standard calibration curves with those obtained from mono-CMIA for each component and yielded excellent agreement. Moreover, a very similar response of all three analytes in single and triple assays was established, further demonstrating the feasibility of the approach.

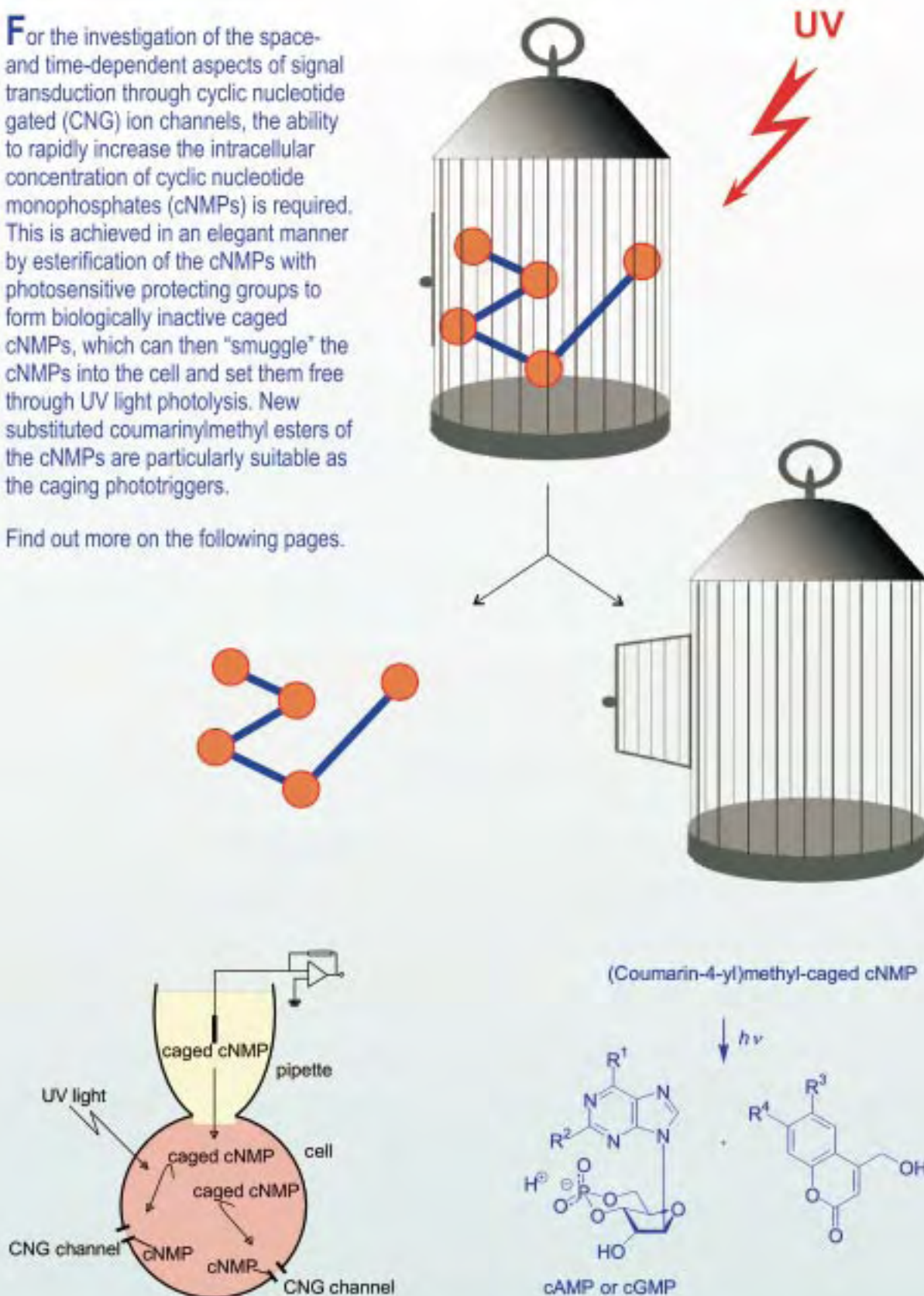
The three examples in this article exemplify an increasing interest in organometallic compounds for investigations on biological or medicinal problems. Although in different areas, they nevertheless have some features in common. The

organometallic fragments react differently from coordination compounds that would be employed in more traditional bioinorganic studies. This way, a labeling of biomolecules is possible at unusual positions (as for **5**) or with unparalleled speed and selectivity (as for **1**). The metal compounds described above are very stable species due to their d^6 low-spin electronic structure with filled t_{2g} orbitals in a pseudo-octahedral environment. As such, they falsify a general wisdom among chemists which has it that organometallic compounds are sensitive towards air and moisture and can be handled safely only in glove boxes or Schlenk flasks. There are surely many more organometallic compounds that will form conjugates with unprecedented properties upon binding to biomolecules. Conceivable are, for example, conjugates of organometallic catalysts with peptides for the design of very specific, highly enantioselective catalysts. New tools for molecular biology may arise from the combination of functional organometallic fragments with oligonucleotides. Conjugates of organometallic compounds with small biologically active peptides or antibody fragments may open a new area in medical diagnosis or treatment of diseases. In all these areas, the quest has just begun.

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For the investigation of the space- and time-dependent aspects of signal transduction through cyclic nucleotide gated (CNG) ion channels, the ability to rapidly increase the intracellular concentration of cyclic nucleotide monophosphates (cNMPs) is required. This is achieved in an elegant manner by esterification of the cNMPs with photosensitive protecting groups to form biologically inactive caged cNMPs, which can then "smuggle" the cNMPs into the cell and set them free through UV light photolysis. New substituted coumarinylmethyl esters of the cNMPs are particularly suitable as the caging phototriggers.

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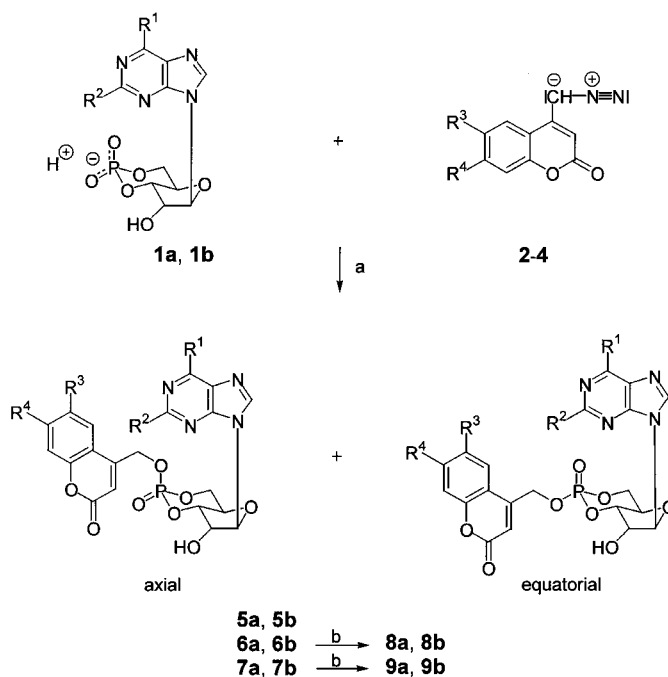
Highly Efficient and Ultrafast Phototriggers for cAMP and cGMP by Using Long-Wavelength UV/Vis-Activation**

Volker Hagen,* Jürgen Bendig, Stephan Frings, Torsten Eckardt, Siegrun Helm, Dirk Reuter, and U. Benjamin Kaupp

The release of the second messengers adenosine 3',5'-cyclic monophosphate (cAMP, **1a**) and guanosine 3',5'-cyclic monophosphate (cGMP, **1b**) from "caged" compounds has proven to be very useful for in situ studies of cyclic nucleotide-dependent cellular processes.^[1] When caged, cAMP and cGMP are rendered biologically inactive by esterification of the phosphate moiety with a photolabile protecting or caging group. Caged biomolecules can be introduced into living cells without evoking any biological response. A flash of light is applied to cleave the caging group and to unmask the biologically active cyclic nucleotide. Thereby, a rapid increase in the intracellular concentrations of cAMP or cGMP can be achieved.

Caged compounds must meet specific requirements. They should be sufficiently soluble in aqueous solutions, stable toward solvolysis, and biologically inert. Furthermore, they should undergo fast and highly efficient photochemical reactions and display high molar absorptivities at wavelengths of >300 nm. The caged cAMPs and cGMPs commonly used up to now do not meet these requirements. The 2-nitrobenzyl,^[2] 4,5-dimethoxy-2-nitrobenzyl (DMNB),^[3] and 1-(2-nitrophenyl)ethyl (NPE) esters^[4] photolyze relatively slowly and display rather low photoefficiencies.^[5] Desoxybenzoinyl-caged (desyl-caged) cAMP^[6] is very sensitive to solvolysis in aqueous buffer solutions^[7] and the (7-methoxycoumarin-4-yl)methyl esters of cAMP and cGMP^[7,8] are poorly soluble.^[9]

Here, we describe caged compounds of cAMP and cGMP exhibiting unprecedented favorable properties. In particular, we focus on the (7-diethylaminocoumarin-4-yl)methyl (DEACM), (7-carboxymethoxycoumarin-4-yl)methyl (CMCM), and [6,7-bis(carboxymethoxy)coumarin-4-yl]methyl (BCMCM) esters of cAMP and cGMP **5a,b**, **8a,b**, and **9a,b**. Their synthesis (Scheme 1) involves treatment of **1a** and **1b** with the diazoalkanes **2–4** followed by diastereomer separation using preparative reverse-phase HPLC and subsequent



- a:** cAMP and coumarinylmethyl-caged cAMPs: $R^1 = \text{NH}_2$, $R^2 = \text{H}$
b: cGMP and coumarinylmethyl-caged cGMPs: $R^1 = \text{OH}$, $R^2 = \text{NH}_2$
- 2, 5:** $R^3 = \text{H}$, $R^4 = \text{NEt}_2$
3, 6: $R^3 = \text{H}$, $R^4 = \text{OCH}_2\text{COO}t\text{Bu}$
4, 7: $R^3 = R^4 = \text{OCH}_2\text{COO}t\text{Bu}$
8: $R^3 = \text{H}$, $R^4 = \text{OCH}_2\text{COOH}$
9: $R^3 = R^4 = \text{OCH}_2\text{COOH}$

Scheme 1. Synthesis of **5–9**: a) DMSO/CH₃CN (1/4), 60 °C, 24 h; b) TFA/CH₂Cl₂/H₂O (75/24/1), RT, 20 min. TFA = trifluoroacetic acid.

deprotection of the *tert*-butoxy groups with trifluoroacetic acid (only necessary for the *tert*-butyl esters). The yields were 11–34% and the diastereomers were formed in approximately 45:55 ratios (axial/equatorial). Isomeric species were assigned by ³¹P NMR spectroscopy. (For preparative details as well as spectroscopic characterization, see Supporting Information.)

The CMCM and BCMCM moieties greatly increase the overall hydrophilicity, and so render the corresponding caged cyclic nucleotides highly soluble in water. This is advantageous for their incorporation into cells, for instance, by standard patch-clamp techniques. The DEACM-protecting group, on the other hand, exhibits remarkable photochemical properties. All novel caged compounds are released very quickly^[10] (within a few nanoseconds) and show very high efficiencies of photocleavage to yield the cyclic nucleotide and the respective strongly fluorescent 4-(hydroxymethyl)coumarin (Scheme 2), due to a combination of high quantum yields and relatively intense absorptivities at >300 nm (Table 1).

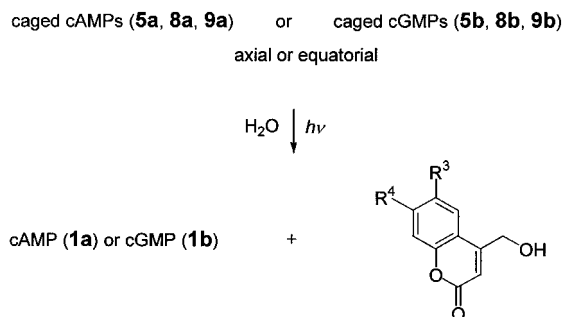
Relative to the values for **8a,b**, the long-wavelength absorption maxima of **9a,b** are red-shifted by approximately 20 nm and those of **5a,b** by as much as 70 nm. Therefore, the optimal wavelengths for the photolysis of **8a,b**, **9a,b**, and **5a,b** are 300–340 nm, 330–370 nm, and 360–440 nm, respectively. As a result, the adaption to conventional continuous wave and

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



Scheme 2. Photolysis of **5a,b**, **8a,b**, and **9a,b**.

Table 1. Long-wavelength absorption λ_{max} , quantum yield Φ of photolysis, and solubility s of the coumarinylmethyl-caged derivatives **5a,b**, **8a,b**, and **9a,b**.

Compound	λ_{max} [nm] (ϵ [$\text{M}^{-1} \text{cm}^{-1}$])	Φ ^[c]	s [μM]
5a (axial) ^[a]	402 (18 600)	0.21 ^[d]	135
5a (equatorial) ^[a]	396 (20 200)	0.23 ^[d]	15
5b (axial) ^[a]	403 (19 300)	0.25 ^[d]	120
5b (equatorial) ^[a]	396 (19 100)	0.26 ^[d]	15
8a (axial) ^[b]	326 (12 500)	0.12	900
8a (equatorial) ^[b]	324 (12 400)	0.10	200
8b (axial) ^[b]	326 (11 700)	0.16	350
8b (equatorial) ^[b]	325 (11 200)	0.10	> 1000
9a (axial) ^[b]	346 (10 700)	0.10	500
9a (equatorial) ^[b]	347 (12 400)	0.08	1000
9b (axial) ^[b]	348 (11 000)	0.14	550
9b (equatorial) ^[b]	347 (11 200)	0.09	> 1000

[a] In acetonitrile/HEPES-KCl buffer (5/95), pH 7.2; $\lambda_{\text{exc}} = 333$ nm. [b] In HEPES-KCl buffer, pH 7.2; $\lambda_{\text{exc}} = 333$ nm. [c] Error limit ± 0.01 . [d] In MeOH/HEPES-KCl buffer (20/80).

laser light sources is straightforward. Solvolytic stability of the novel caged compounds is extremely high with half-lives of >1000 h in HEPES buffer at pH 7.2 (HEPES = 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid). The respective diastereomers of the novel coumarinylmethyl-caged compounds differ only in their solubility in aqueous buffer solutions (Table 1), and at least in the case of **5a,b**, the use of the more soluble isomer is recommended.

In Table 2 the efficiencies of photorelease of the axial isomers of **5b**, **8b**, and **9b** in comparison to DMNB- and NPE-caged cGMP in aqueous buffer solution at different wavelengths are illustrated. The results show that the coumarinylmethyl-caged compounds are far superior to the nitrobenzyl-caged derivatives. The highest release of cGMP is achieved with the following caged compounds: at 337 nm (HBO, nitrogen laser) with **8b**, at 365 nm (HBO, argon-ion laser)

with **9b** and **5b**, and at 405 nm (HBO) with **5b** (HBO = high pressure lamp, Osram).

The excellent properties of the novel caged compounds were confirmed in studies on cyclic nucleotide-gated (CNG) channels using the patch-clamp method. In HEK293 cells expressing cAMP-gated channels (CNCa3), submaximal activation of the channels was obtained with **9a** and illumination at 360 nm by flashes of 20 ms duration; maximal activation was achieved by a 100 ms flash (Figure 1). In Figure 2 the photorelease of cyclic nucleotides from **9a** is

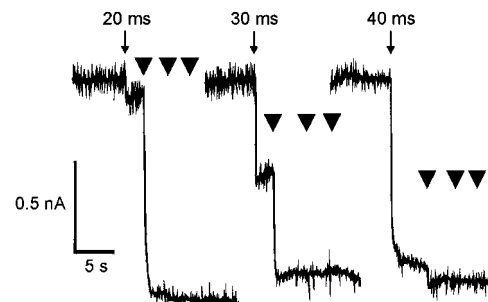


Figure 1. Determination of the concentration of photolytically released cAMP from the activation of cAMP-gated ion channels in HEK293 cells. (Whole-cell current recordings at -70 mV obtained from three cells that were loaded with $500 \mu\text{M}$ of the equatorial isomer of **9a**.) Brief flashes of UV light (20–40 ms, $\downarrow$) do not liberate sufficient cAMP to maximally activate the channels. Longer flashes (100 ms, $\blacktriangledown$) induce maximal channel activity. The relative current amplitude at submaximal activation is used to calculate the concentration of photoreleased cAMP using the known dose–response relationship for channel activation by cAMP.^[11]

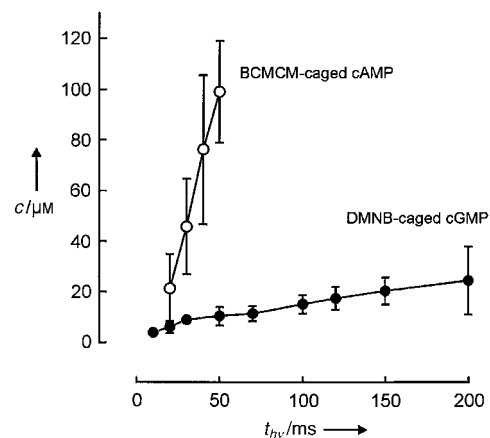


Figure 2. Comparison of photolytic liberation of cyclic nucleotides from **9a** and DMNB-caged cGMP in HEK293 cells at various flash durations. Due to better solubility and quantum yield, BCMCM derivatives can produce tenfold higher concentration steps. c = concentration of free nucleotide, t_{flash} = duration of flash.

Table 2. Comparison of the efficiencies (in %) of the release of cGMP from caged compounds (axial isomers) with various irradiation times at different wavelengths.

Compound	t ($\lambda_{\text{exc}} = 333$ nm)			t ($\lambda_{\text{exc}} = 365$ nm)			t ($\lambda_{\text{exc}} = 405$ nm)		
	6 s	60 s	600 s	6 s	60 s	600 s	6 s	60 s	600 s
NPE ester ^[a]	2	7	38	<1	2	10	<1	<1	1
DMNB ester ^[a]	<1	3	10	<1	3	11	<1	<1	<1
5b (DEACM ester) ^[a]	3	15	75	16	80	>98	38	98	>98
8b (CMCM ester) ^[b]	16	75	>98	4	19	93	<1	1	3
9b (BCMCM ester) ^[b]	10	51	98	12	65	>98	1	3	20

[a] $c = 25 \mu\text{M}$ in MeOH/HEPES (1/4). [b] $c = 25 \mu\text{M}$ in HEPES.

compared with that from DMNB-caged cGMP in HEK293 cells expressing cAMP-gated (CNC α 3) and cGMP-gated (CNC α 2) channels. The cells were loaded with 500 μ M of the equatorial isomer of **9a** or 200 μ M (maximal solubility) of the axial isomer of DMNB-caged cGMP using a patch pipette and illuminated with UV rays. The nucleotide concentrations released by the flash were estimated using the known dose–response relation for activation of the channels by cAMP and cGMP.^[11] The experiment demonstrates that **9a** liberates the cyclic nucleotide about one order of magnitude more efficiently than the DMNB-caged derivative and that only **9a** is able rapidly to produce high concentrations of cyclic nucleotide inside cells. In Figure 3 the photorelease at $\lambda = 405$ nm of 8-Br-cGMP from the axial isomer of DEACM-

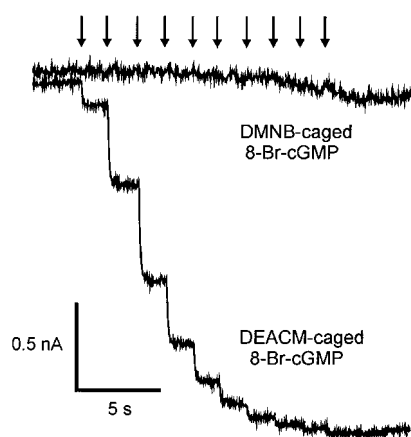


Figure 3. Activation of cGMP-gated cation channels by 8-Br-cGMP photolytically liberated from caged derivatives through a series of 5-ms UV light flashes (405 ± 20 nm, $\downarrow$). (Whole-cell current recordings from two HEK293 cells at -50 mV with 20μ M of the respective caged compound.)

caged 8-Br-cGMP^[12] is compared with that from the axial isomer of DMNB-caged 8-Br-cGMP^[11] in HEK293 cells expressing CNC α 2 channels. While every light flash released approximately 0.5μ M of cGMP from the DEACM-caged compound, no measurable release could be detected with the DMNB-caged compound.

The properties of the caged compounds inside cells correspond well with their performance in solution and confirm that the described coumarinylmethyl-caged compounds are indeed highly efficient phototriggers for cAMP and cGMP. The advantage of the carboxymethoxy-substituted coumarinylmethyl esters **8a,b** and **9a,b** arises from their superior solubility allowing the instantaneous liberation of high concentrations of the cyclic nucleotides. With respect to the DEACM-caged compounds **5a** and **5b**, the cyclic nucleotides are efficiently released under nondamaging light conditions. In summary, these novel caged compounds show great potential for the study of spatial- and time-dependent aspects of cellular signaling at a quantitative level.

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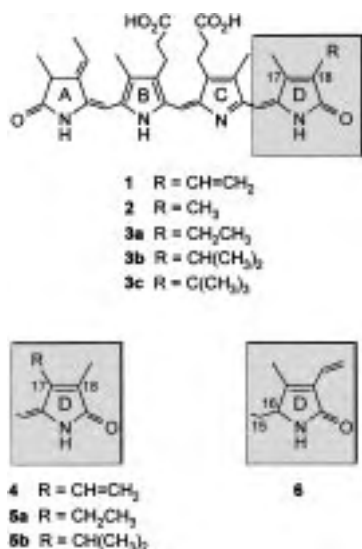
Analysis of the Topology of the Chromophore Binding Pocket of Phytochromes by Variation of the Chromophore Substitution Pattern

Uwe Robben, Ingo Lindner, Wolfgang Gärtner,* and Kurt Schaffner

*Dedicated to Professor Henning Hopf
on the occasion of his 60th birthday*

We have recently reported^[1] on the use of synthetic linear tetrapyrroles with modified substitution patterns on ring D in recombinant phytochromes (65 kDa oat phyA),^[2] in order to spectroscopically explore the interactions between the binding pocket of the protein and the chromophores phytochromobilin (**1**; Scheme 1), isophytochromobilin (**4**), and phycocyanobilin (**3a**). The first unnatural chromophore investigated (**4**)^[1] has been found, upon assembly with the recombinant apoprotein (apophyA65),^[3] to undergo a $P_r \rightarrow P_{fr}$ photoisomerization which is characteristic of phytochromes such as phyA65-1. The absorption maximum for the P_{fr} form of phyA65-4 is hypsochromically shifted by about 14 nm. This shift occurs selectively in the P_{fr} form and is even larger (by

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Scheme 1. Structural formulas of naturally occurring (**1**, **3a**, **6**) and synthetic (**2**, **3b**, **c**, **4**, **5a**, **b**) open-chain tetrapyrroles which have been assembled with recombinant oat apophytochrome (phyA65): phytochromobilin (**1**), phycocyanobilin (**3a**), phycoerythrobilin (**6**), isophytochromobilin (**4**), isophycocyanobilin (**5a**), and the 17,18-dimethyl **2**, 17-methyl-18-isopropyl **3b**, 17-methyl-18-*tert*-butyl **3c**, and 17-isopropyl-18-methyl **5b** derivatives of **3a**.

3 nm) than in phyA65-**3a** (Table 1). In chromoprotein phyA65-**3a** the absorptions of both P_r and P_{fr} are blue shifted with respect to phyA65-**1**, presumably due to the saturation of the vinyl group at C18. The question remained, to what extent are these differences in the absorption maxima to be attributed to steric or electronic effects, or a subtle interplay of both.

Table 1. Assembly kinetics[a] of recombinant oat apophytochrome, apo-phyA65, with linear tetrapyrroles and phyA65 absorption maxima λ_{max} of the assembled holoproteins.

Tetrapyrrole component	τ_1 [a] [min]	τ_2 [a] [min]	$\lambda_{\text{max}}(P_r)$ [nm]	$\lambda_{\text{max}}(P_{fr})$ [nm]
phytochromobilin (1)	0.38	2.93	665 ^[b]	728 ^[b]
iso-phytochromobilin (4)	3.02	19.6 ^[b]	663 ^[b]	714 ^[b]
17,18-dimethyl homologue 2	1.62	10.8	655	714
phycocyanobilin (3a)	0.88	10.6	653 ^[b]	717 ^[b]
17-methyl-18-isopropyl homologue 3b	6.14	51.6	650	718
17-methyl-18- <i>tert</i> -butyl homologue 3c	13.2	58.6	651	719
17-ethyl-18-methyl homologue 5a	7.64	43.8	658	707
17-isopropyl-18-methyl homologue 5b	10.5	156	550	705
phycoerythrobilin (6)	— ^[c]	— ^[c]	576 ^[d]	n.a.

[a] The measured absorption increases (at λ_{max}) were fitted to biexponential kinetics. $\tau = 1/k$. [b] From ref. [1]. [c] For the assembly kinetics of **6** with apophyA124, see ref. [6]. [d] From ref. [6]. n.a. = not available.

We have addressed this question by assembling apophyA65 with the linear tetrapyrroles **2**, **3b**, **c**, and **5a**, **b**, in which the steric requirements of alkyl substitution on ring D (at C17 and C18) systematically vary. The P_r/P_{fr} absorption spectra, the assembly kinetics, and the kinetics of the thermal P_{fr} back-isomerization were all investigated as a function of the C17 and C18 substituents, in order to probe the steric constraints associated with the conformationally induced protein–chromophore interactions that are brought about by the C15–C16

double bond photoisomerization. The results complement the earlier study employing the tetrapyrroles **1**, **3a**, and **4**,^[1] and supplement the data for the two homologous series **2/3a/3b/3c** and **2/5a/5b**.

All newly assembled chromoproteins, phyA65-**2**, -**3b**, **c** and -**5a**, **b**, underwent the phytochrome photochromic cycle (Table 1 and Figure 1). The chromoproteins carrying the

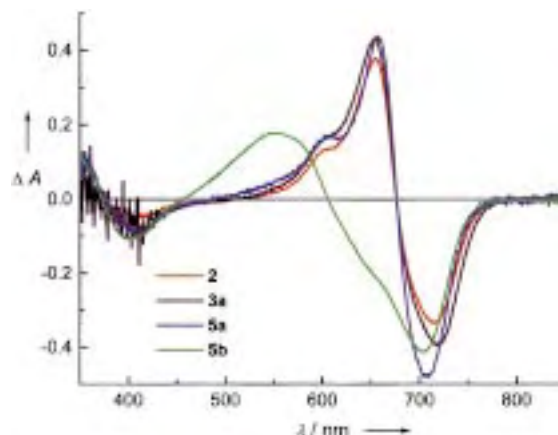


Figure 1. Difference spectra $A(P_r) - A(P_{fr})$ of recombinant oat phyA65 phytochromes, assembled with phycocyanobilin (**3a**) and its 17,18-dimethyl **2**, 17-ethyl-18-methyl **5a**, and 17-isopropyl-18-methyl **5b** derivatives.

C18-modified tetrapyrroles, PhyA65-**2** and -**3a–c**, all exhibit very similar P_r - and P_{fr} -like absorption maxima. This is quite in contrast to the absorptions of the 17-ethyl and 17-isopropyl homologues, phyA65-**5a** and -**5b**, respectively. While the P_r -like form of phyA65-**5a** still absorbs within the range of phyA65-**2** and **3b**, **c**, all other absorptions are appreciably shifted to shorter wavelengths: the shifts of the P_{fr} -like forms of phyA65-**5a** and -**5b** are around 10 nm and, in particular, the maximum of the P_r -like form of phyA65-**5b** is shifted by a dramatic 100 nm.

The biexponential kinetics of the chromophore incorporation reflect a similarly selective influence by substituent size and position (Table 1). Interestingly, the naturally occurring 17-methyl-18-ethyl derivative **3a** is, after **1**, assembled fastest. While the 17,18-dimethyl compound **2** is assembled only slightly slower than **3a** with respect to τ_1 , in both homologous series, **2/3b/3c** and **2/5a/5b**, the increasing steric crowding clearly slows down the assembly rates τ_1 and τ_2 , with the isopropyl substituent at C17 yielding the strongest effect on τ_2 . In every case, the P_r form is recovered upon $P_r \rightarrow P_{fr}$ photorecycling. Although some of the spectral shifts among the homologous chromoproteins are very large, these are all best reconciled by the assumption that they are due to differences in chromophore–protein interactions rather than to regiochemical differences in the chromophore binding to the protein.

The thermal isomerization of the photochemically generated P_{fr} form back to the P_r form^[4] also correlates with the size of the substituents on ring D of the chromophore. The thermally most stable chromoprotein is the one with the bulkiest substituent, *tert*-butyl (phyA65-**3c**), while the C17-modified chromophores phyA65-**5a** and -**5b** markedly accelerate the thermal isomerization to the P_r form (Figure 2).

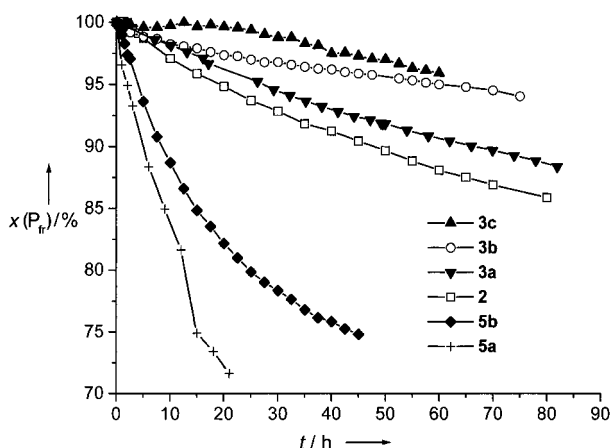


Figure 2. Kinetics of the thermal $P_{fr} \rightarrow P_r$ isomerization of the recombinant phyA65-2, -3a-c, and -5a,b phytochromes at ambient temperature. The P_{fr} samples were prepared by saturating irradiation of the corresponding P_r forms.

The steric interactions between ring D of the chromophore and the amino acids of the protein pocket significantly influence the rates of the chromophore binding to the apoprotein and the thermal reversal of P_{fr} to P_r . Relative to phytochromes with a native chromophore, which possess a C_1 substituent at C17 and a C_2 substituent at C18 (such as phyA65-1 and -3a), the changes in reactivity depend on the position of the substituent(s) modified, C17 or C18, with C17 being more sensitive. Thus, the assembly of the 17-ethyl and 17-isopropyl homologues 5a and 5b is clearly slower than that of the respective C18 regioisomeric analogues 3a and 3b. The extreme blue shift of the P_r form of phyA65-5b ($\lambda_{max} = 550$ nm) may reflect a particularly strong steric constraint by the protein, which forces ring D of the chromophore out of plane with regard to rings A–C and thus interrupts conjugation of the π system.^[5] A blue shift in absorption which is almost as large ($\lambda_{max} = 576$ nm) has also been observed for phyA124-6,^[6] brought about upon interruption of conjugation due to the 15,16-saturated bridge between rings C–D of the phycoerythrobilin chromophore 6. Whereas 6 cannot form a P_{fr} because of the saturated C15–C16 bond, we find for P_{fr} of 5b only a moderately blue-shifted maximum (see Table 1). As another reason for the blue shift, a weakening of the protonation state, for example, by an increase of the distance between proton donor and chromophore, appears possible. In this context a decrease in absorption to accompany the blue shift would be expected upon deprotonation of the chromophore, as in the transition from the 17-ethyl (5a) to the 17-isopropyl isomer (5b).

Experimental Section

Synthesis of the linear tetrapyrroles 2, 3b, c, and 5a, b:

The total syntheses of the new tetrapyrroles followed the convergent strategy of A-B+C-D $\rightarrow$ A-B-C-D previously described.^[7] The various ring D substitution patterns were made accessible by adaptation of a previously developed pyrrole synthesis^[8] based on addition of an aldehyde to a nitroalkane, acetylation, and coupling with *tert*-butyl isocyanacetate.

The oxidation of 2,5-unsubstituted pyrroles to pyrrol-2-ones^[9] was not regioselective. Both regioisomers resulting from the unsymmetrically

substituted pyrroles could be used separately after chromatographic separation for the synthesis of the two homologous series of tetrapyrroles.

While all the 4-methylpyrrol-2-ones coupled with the ring C component in good yields, the 4-isopropyl homologue was obtained in very low yield, probably due to steric crowding. Attempts to achieve coupling with the 4-*tert*-butyl derivative failed entirely.

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Isolated Hexagonal Channels Built up by Three-Connected Ge[−] Ions in LiGe at High Pressure**

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In the homologous series of LiE compounds (E = Group 14 elements Si–Pb), LiSi^[1, 2] and LiGe^[3, 4] are Zintl phases at normal pressure (NP),^[5, 6] but LiSn^[7] and LiPb^[8, 9] belong to the class of intermetallic phases. Owing to a charge transfer Li⁺Si[−] and Li⁺Ge[−], the Si[−] and the Ge[−] ions in these Zintl phases are isovalence-electronic to the elements of Group 15, and build up the three-dimensional three-coordinate net of the MgGa-type structure^[10] with three homonuclear bonds. However, in the intermetallic compounds LiSn^[7] and LiPb,^[8, 9]

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the Sn atoms have four and six homonuclear contacts, respectively. Therefore due to the change of bonding within these series of LiE compounds, LiGe and LiSn are ambivalent compounds and one can expect a shift in bonding if different temperatures and pressures are applied. Treatment of NP-LiGe at 4 GPa and 600 °C in a belt apparatus is sufficient to prepare a tetragonal LiGe high-pressure (HP) phase,^[11] in which there are twice as many two-coordinate Ge²⁻ ions as four-coordinate Ge⁰ atoms. The electron balance demands a total of 16e⁻ for two Ge²⁻ ions (2 × 6 = 12 valence electrons e⁻) and one Ge⁰ atom (4e⁻); however, in 3LiGe there are only 15e⁻ available. The Zintl phase NP-LiGe is transformed into a “near-Zintl-phase”^[12] The opposite effect is observed for NP-LiSn. Slowly cooling a LiSn melt leads to the thermodynamically stable intermetallic phase α -LiSn.^[7] However, if a Li-Sn-Ga melt is cooled, β -LiSn^[13] is obtained, which is isotypic with the tetragonal phase HP-LiGe and thus also a “near-Zintl-phase”.

Surprisingly, it is also possible to prepare a second hexagonal HP LiGe phase in a belt apparatus at 4 GPa and 900 °C. This phase is also quenchable to ambient conditions. Crystallographic data for the three LiGe phases are presented in Table 1. Inspection of this table shows that there is only a small difference in density and in unit cell volume between the hexagonal and the tetragonal HP phases of LiGe. The increase in density in relation to the NP phase is 9.6% for tetragonal HP-LiGe and 9.2% for hexagonal HP-LiGe.

Table 1. Crystallographic data of the three LiGe phases.^[3, 4, 11]

	LiGe(ND)	LiGe(HD)	LiGe(HD)
crystal system	tetragonal	tetragonal	hexagonal
space group	<i>I</i> ₄ /a	<i>I</i> ₄ /amd	<i>P</i> ₆ ₃ /mmc
<i>a</i> [Å]	9.810(3)	4.0529(1)	8.451(3)
<i>c</i> [Å]	5.807(2)	23.282(3)	6.198(3)
<i>V</i> [Å ³]	558.8(4)	382.4(1)	383.4(4)
<i>Z</i>	16	12	12
ρ_{calcd} [g cm ⁻³]	3.782	4.145	4.135

Table 2 gives the number of neighbors, interatomic distances, and Ge-Ge-Ge bond angles. In both the NP-LiGe and hexagonal HP-LiGe phases, Ge atoms form three homonuclear bonds.

Therefore both are Zintl phases consisting of Li⁺ and Ge⁻ ions, in contrast to tetragonal HP-LiGe, which is, as already mentioned, only a “near-Zintl phase” with twice as many two-coordinate as four-coordinate Ge atoms. The Ge⁻ ions in hexagonal HP-LiGe build up puckered six-membered rings of distorted chairs, which are stacked above each other (Figure 1a). The Ge-Ge bonds in the chair are 2.55 Å long and form angles of 116° (Table 2). The third Ge-Ge bond (2.56 Å) connects the chair with adjacent chairs alternating up or down (Figure 1a); the Ge-Ge-Ge angle is 102°. This leads to puckered six-membered rings of distorted boats; ideal chairs and boats have bond angles of 109.5°. Figure 1b shows a

Table 2. Number of neighbors, interatomic distances [Å],^[a] and Ge-Ge-Ge angle [°].^[3, 4, 11]

	LiGe(ND) tetragonal	LiGe(HD) ^[b] tetragonal	LiGe(HD) hexagonal
Ge neighbors	3 Ge: 2.560(2 ×), 2.655(1 ×) 8 Li: 2.66, 2.73, 2.77, 2.82, 3.07, 3.11, 3.17, 3.54	4 Ge _{II} : 2.70 2 Ge _I : 2.70 8 Li(Ge _I): 2.87(4 ×), 2.88(4 ×) 8 Li(Ge _{II}): 2.70(2 ×), 2.84(2 ×), 2.88(4 ×)	3 Ge: 2.55(2 ×), 2.56(1 ×) 8 Li: 2.71, 2.73(2 ×), 2.80, 3.00, 3.02(2 ×), 3.09
Ge-Ge-Ge [°]	105, 109, 117	Ge _I : 97(2 ×), 116(4 ×) Ge _{II} : 97	102(2 ×), 116
Li-Li [Å]	2.91, 2.97	2.66, 2.88	2.44, 2.71, 2.73, 3.00, 3.02, 3.09, 3.10

[a] Standard deviation [Å]: NP-LiGe: Ge-Ge, Li-Ge: ± 0.005; Li-Li: ± 0.01; HP-LiGe tetragonal: Ge-Ge: ± 0.01, Li-Ge: ± 0.03, Li-Li: ± 0.05; HP-LiGe hexagonal: Ge-Ge: ± 0.01, Li-Ge: ± 0.05, Li-Li: ± 0.08. [b] Tetragonal HP-LiGe^[11] contains four four-connected (Ge_I) and eight two-connected Ge atoms (Ge_{II}) as well as four Li atoms in the centers of the Ge eight-membered rings (Li_I) and eight Li atoms above or below the two-connected Ge atoms (Li_{II}).

perspective view along [001] (the stacking axis) of the hexagonal HP-LiGe phase which reveals a new motif: three-connected Ge⁻ ions build up hexagonal channels. These channels, centered at the corners of the unit cell, are 4.13 Å apart, a distance more than 1.6 times the Ge-Ge bond length. Such an arrangement of isolated hexagonal channels built up by three-coordinate ions is observed here for the first time for a Zintl phase. Li⁺ counterions are found in the center of the hexagonal channels and in the symmetry-equivalent positions between them.

Figure 1c, d shows clearly that tetragonal HP-LiGe^[11] has a layer structure with a sequence of four layers each consisting of two- and four-coordinate germanium. One third of the Li⁺ counterions are found in the center of the Ge eight-membered rings, one third lie above and one third lie below the two-coordinate Ge²⁻ ions. Figure 1e depicts the three-dimensional net of three-coordinate Ge⁻ ions in NP-LiGe,^[3, 4] in which puckered eight-membered germanium rings are arranged along fourfold screw axes. Six such puckered Ge eight-membered rings are shown which are connected by two fourfold counterrotating screw axes (4₃, 4₁). In each Ge eight-membered ring there are four Li⁺ counterions in a distorted tetrahedral arrangement.

In all three LiGe phases each germanium atom has eight Li neighbors (Table 2), and each lithium atom has eight Ge neighbors (not shown in Table 2), leading to 8:8 coordination. Whereas in the NP-LiGe phase the Ge-Li distances range between 2.66 and 3.54 Å, in both HP phases this range is smaller (2.70–2.88 Å for the tetragonal and 2.71–3.09 Å for the hexagonal phase). Additionally, Table 2 shows that many of the Li-Li distances in the HP phases are shorter than those in the NP phase. The shortest Li-Li distance is 2.91 Å in the NP phase, 2.66 Å in the tetragonal HP phase, and 2.44 Å in the hexagonal HP phase.

In addition to the 8:8 coordination for the three LiGe phases, there is another common feature. All three phases

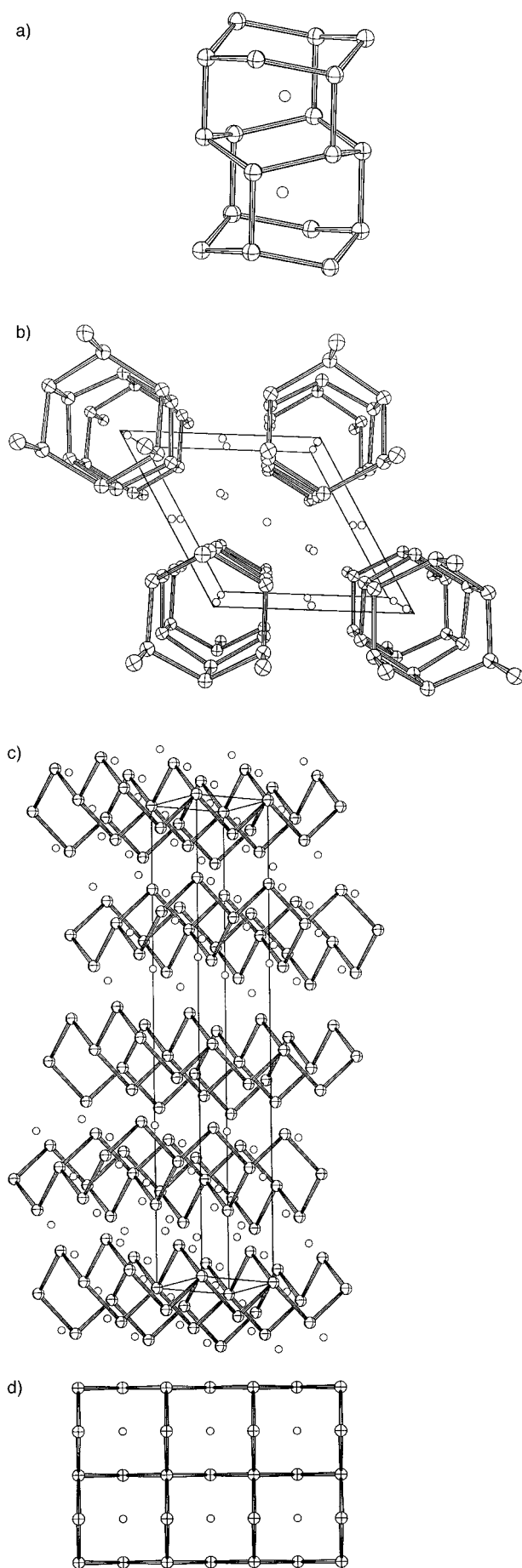


Figure 1. ORTEP plots for the three LiGe phases. a) View along a section of a hexagonal channel (large circles with a cross: Ge, small circles: Li) of hexagonal high-pressure phase. b) Perspective view along [001] of the hexagonal HP phase. c) Layer structure of the tetragonal HP phase.^[11] Here only a section with six eight-membered rings comprising two- and four-coordinate Ge atoms per layer is shown; for reasons of clarity the Li⁺ ions were omitted from the central layer. d) One Ge layer of the tetragonal HP phase (view along [001]); a Li⁺ ion is located in the center of each eight-membered ring. e) The tetragonal NP phase (view along [001]).^[3, 4] For details see text.

show a structural motif which is reminiscent of elemental germanium. Cubic germanium (3C-Ge) consists of four-connected atoms that build puckered six-membered rings of ideal chairs, which are stacked in the [111] direction with a repeat unit of three layers. Puckered eight-membered rings of four-connected atoms are stacked along the cubic axes. Both tetragonal phases NP-LiGe and HP-LiGe contain puckered eight-membered rings, in contrast hexagonal HP-LiGe has puckered six-membered rings. In NP-LiGe these eight-membered rings are connected to form a three-dimensional net along [001] (Figure 1e), whereas in the tetragonal HP-LiGe phase they are arranged parallel (001) and build up a layer structure (Figure 1c, d). In the hexagonal HP-LiGe phase the puckered six-membered rings lie directly above each other, in elemental 3C-Ge they are shifted towards each other leading to a repeat unit of three layers (Figure 1b). Analogous to hexagonal wurtzite as well as diamond with a sequence of two layers, hexagonal germanium (2H-Ge, $a = 3.94(5)$, $c = 6.55(5)$ Å)^[14] consists of six-membered rings of chairs that lie directly above each other. This arrangement also leads to boats as in HP-LiGe. Compared to 2H-Ge, in hexagonal HP-LiGe the a axis is doubled and additionally increased by 6%, whereas the c axis is slightly decreased by 5% (Table 1). Therefore, hexagonal HP-LiGe can be derived simply from 2H-Ge by doubling the a axis, then removing the four Ge atoms connecting the germanium chairs within the same layer, and finally filling the Li ions into the channels and into the symmetry-equivalent positions between them!

Experimental Section

NP-LiGe, which was prepared by melting Li and Ge in a water-cooled copper boat under argon, was converted into the HP phase in a belt apparatus in boron nitride and molybdenum crucibles at typically $p = 4$ GPa, $T = 900$ °C. After 20 min, the heating was stopped and the pressure was released 5 min later. Heating the new phase at 1 bar to 300 °C led in an exothermic reaction quantitatively to the thermodynamically stable NP phase. X-ray photographs of a crystal of the new HP phase ($\text{CuK}\alpha$ radiation)

showed Laue symmetry $6/mmm$ (systematic absences: hkl with $l = 2n$) and the lattice parameters $a = 8.45$, $c = 6.20$ Å. However, the quality of the crystal was not sufficient to perform a structure determination on a four-circle diffractometer. Therefore structural parameters were determined on powder material with a Guinier diffractometer. The approximate Ge and Li positions were derived from Patterson and Fourier syntheses.^[15] Refinement was performed by the Rietveld method.^[16–18] Hexagonal HP-LiGe was obtained as a phase mixture with 20% germanium (calculated from the scaling factors^[19] of the Rietveld refinement). Owing to the extreme conditions in the preparation, the mobile Li^+ ions show high thermal parameters.^[18]

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A New Phase-Switch Method for Application in Organic Synthesis Programs Employing Immobilization through Metal-Chelated Tagging**

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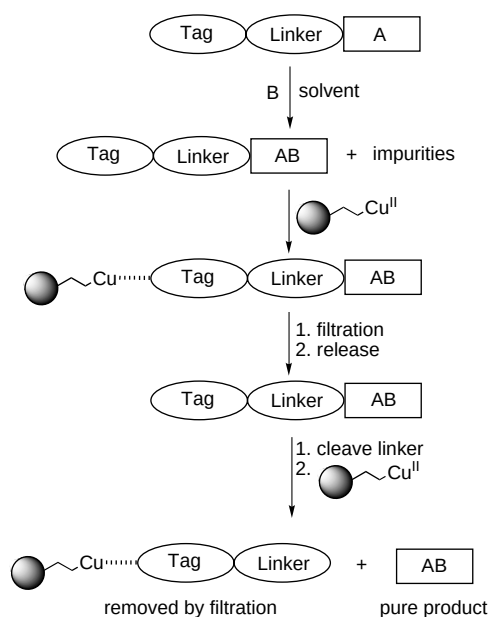
The increasing demand for large numbers of new compounds for biological testing has encouraged synthetic chemists to look for new technologies and strategies to produce these compounds in a fast, clean, and efficient way. Presently, the most popular way in which this can be achieved is by the use of solid-phase organic synthesis (SPOS). This methodology allows the use of an excess of reagents and at the end of the synthetic sequence the immobilized product is isolated following a simple filtration.^[1] Unfortunately, there are considerable limitations to this approach: The reactions are often slower than their solution-phase counterparts, it is difficult to monitor the reaction progress, and long optimization times are often required to transfer solution-phase chemistry onto the polymer support. Owing to these limitations, new strategies combining the benefits of established protocols for solution-phase chemistry with the key advantages of solid-phase chemistry are being developed which allow multistep syntheses to be performed using an array of supported reagents and scavenging agents.^[2] One particular feature of combinatorial chemistry programs is the challenge of product purification by using methods which can be automated and operated in a multiparallel mode.^[3]

Herein we report a new strategy for the synthesis of small-molecule libraries based on the “catch and release” principle.^[4] In this approach we have devised a method of *selectively and reversibly* immobilizing key intermediates within a conventional solution-phase-mediated reaction sequence. We argued that a phase switch/separation^[2] could be effected by a reversible and selective noncovalent interaction between a resin-bound metal and an organic metal-chelating “tag” linked to the molecule of interest (Scheme 1).^[5] Thus, the immobilization or “phase switching”^[2] of the tagged intermediate upon completion of the solution-phase reaction would be realized by the addition of a resin-bound metal to

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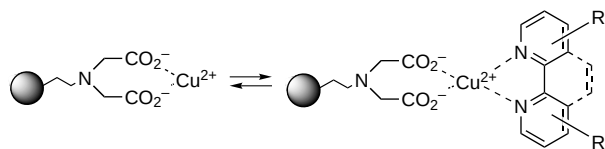
[**] We gratefully acknowledge financial support from Pfizer Global Research and Development, the University of Ferrara (Italy, Postdoctoral Fellowship to A.M.), the EU (Marie Curie Fellowship to F.R.), and a Novartis Research Fellowship (to S.V.L.).



Scheme 1. Strategy devised for the synthesis and purification of small-molecule libraries.

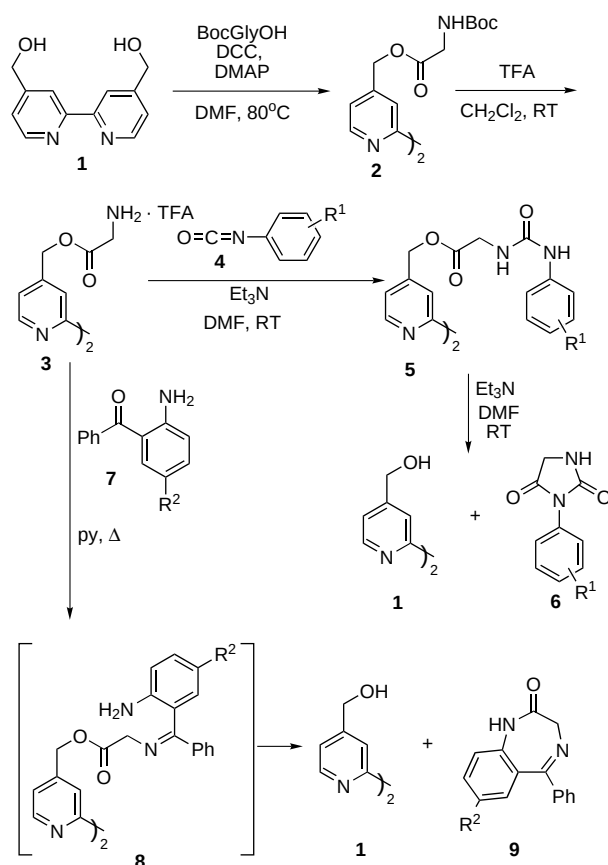
the reaction media to act as an insolubilizing agent by complex formation. The resin would be washed, to remove excess reagents and by-products, and finally the purified intermediate would be easily obtained after release from the resin. Moreover, the appropriate choice of the tag would allow the tagged intermediate to be isolated and purified through a simple process of precipitation and filtration.^[6] The final stage of the scheme requires controlled cleavage of the tag to yield the desired molecule.

A variety of transition metals, metals bound to solid supports, and metal-chelating organic molecules were evaluated. The preferred resin, however, with respect to optimal loading of copper(II) ions was found to be the inexpensive solid support IRC-718 which contains iminodiacetic acid.^[7] Of the various metal-chelating “tags” explored bidentate pyridine-containing ligands such as 1,10-phenanthroline and 2,2'-bipyridine were found to be optimal, not only with respect to their good affinity for copper(II) ions but also in regard to their moderately low reactivity to a wide range of reaction conditions (Scheme 2).



Scheme 2. Capture of bipyridine-tagged molecules by copper(II)-containing beads.

The preparation of a series of hydantoins and benzodiazepines was chosen to evaluate the method, since a solid-phase synthesis of these moieties had been previously reported.^[8] For the synthesis of these compounds 4,4'-bis(hydroxymethyl)-2,2'-bipyridine (**1**) was found to be a suitable tag (Scheme 3).^[9] The hydroxyl groups of this molecule constitute



Scheme 3. Synthesis of hydantoins **6** and benzodiazepines **9**. DCC = dicyclohexylcarbodiimide, DMAP = dimethylaminopyridine, DMF = *N,N*-dimethylformamide, py = pyridine.

the linker component, which can be easily decorated with various synthesis elements. For example, acylation of **1** with *N*-*tert*-butoxycarbonylglycine under standard amide-coupling conditions gave the bisglyciny ester **2** in solution. This was then captured by the addition of copper(II) ions bound to IRC-718 beads, which were then washed to remove excess reagents and other by-products. Diester **2** was released from the beads by the addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and shaking the suspension for 8 h.^[10] Filtration and concentration of the filtrates afforded diester **2** in 70 % yield and >95 % purity, as established by ¹H NMR spectroscopy. Both the uptake and release of **2** could be easily monitored by thin-layer or high-performance liquid chromatography. The *tert*-butoxycarbonyl (Boc) group was subsequently removed using trifluoroacetic acid (TFA), and after evaporation of excess reagent the bis-TFA salt **3** was obtained quantitatively. This salt was then treated with a variety of isocyanates **4** to give crude urea derivatives **5**.

Two different procedures were used for the purification of the urea derivatives. First, the beads of resin-bound copper(II) ions were added to the crude solution of the urea derivative **5b** and after the “catch-release” technique described above **5b** was isolated in 85 % yield (>95 % purity). Secondly, it was found that urea derivatives **5a–f** precipitated from the reaction media by the simple addition of a mixture of petrol ether and ethyl acetate. This process gave the products in very high yields and in purities greater than 90 % following a

simple procedure of precipitation followed by filtration (Table 1, entries 1–6).^[6] With compounds **5a–f** in hand, the final step of cyclization and release of the tag was performed

Table 1. Ureas **5**, hydantoins **6**, and benzodiazepines **9** prepared according to Scheme 3. The purities given in brackets (in %) next to the yields were determined by ¹H NMR spectroscopy.

Entry	R ¹ or R ²	5	Yield ^[a]	6	Yield ^[b]	9	Yield ^[a]
1	H	5a	94 (>95)	6a	91 (>95)		
2	4-CF ₃	5b	93 (>95) ^[c]	6b	93 (>95)		
3	4- <i>i</i> Pr	5c	96 (>92)	6c	99 (>95)		
4	4-F	5d	97 (>95)	6d	99 (>92)		
5	4-Br	5e	97 (>90)	6e	99 (>95)		
6	3-SMe	5f	96 (>95)	6f	97 (>95)		
7	H					9a	51 (>90)
8	Cl					9b	49 (>90)

[a] Based on the TFA-diester **3**. [b] Based on the starting urea **5**. [c] A yield of 85 % (>95 % purity) was obtained after purification using the procedure based on the beads of resin-bound copper(II) ions (see text).

using triethylamine. Tag **1** was immobilized using the beads of resin-bound copper(II) ions and after filtration and concentration of the filtrates hydantoins **6a–f** were obtained in yields and purities higher than 90 % (Scheme 3 and Table 1, entries 1–6). Moreover, this technique allowed us to quantitatively recover and reuse the tag **1** after it was released from the beads of resin-bound copper(II) ions with TMEDA.

Benzodiazepines **9** were synthesized in a similar fashion. Intermediate **3** was heated with aminoketones **7** in pyridine for three–five days. In situ cyclization of intermediates **8** gave benzodiazepines **9** in addition to the released tag **1** (Scheme 3). The mixture was then treated with the copper(II)-containing beads to remove the tag, and after filtration and removal of solvents benzodiazepines **9a, b** were obtained with high levels of purity in moderate yields (Table 1, entries 7–8). In these cases it was also possible to recover the tag **1** and reuse it in further reactions.

In summary, we have described a new strategy for the parallel synthesis of small molecules that combines the advantages of both *solution-* and *solid-phase* organic synthesis. The principal advantages of such an approach include: 1) minimal optimization is required and as a consequence of the process being performed in solution the progress of the reaction can be monitored by simple, well-established procedures such as thin-layer chromatography and liquid chromatography, and 2) immobilization of key intermediates onto the polymeric beads facilitates purification by simple filtration. Moreover, the use of bipyridine tags allows purification of some intermediates by precipitation and filtration. This procedure could also be adapted to split-and-mix syntheses. Further studies including the use of other organic metal-chelating “tags” as scavengers and reagents are underway.

Experimental Section

Preparation of hydantoin **6c** from **3**: Triethylamine (0.28 mmol) and 4-isopropylphenyl isocyanate (0.56 mmol) were added to a solution of **3** (0.07 mmol) in DMF (0.5 mL) at room temperature. After stirring the mixture for 30 min, a 1:1 mixture of petrol ether and ethyl acetate (4 mL) was added, and the resulting solid was filtered and washed with petrol ether

(2 mL) to obtain urea **5c** (96 % yield, >92 % purity). Compound **5c** was dissolved in DMF (1 mL) and triethylamine (0.5 mL) was added. After stirring the mixture for 3 days it was diluted with dichloromethane (2 mL). Beads of resin-bound copper(II) ions (0.5 g) and 3 drops of water were added, and the mixture was shaken for 30 min. Filtration and removal of the solvents afforded **6c** (99 % yield, >95 % purity). ¹H NMR (400 MHz, CDCl₃): δ = 7.26 (d, *J* = 8.5 Hz, 2H; ArH), 7.23 (d, *J* = 8.5 Hz, 2H; ArH), 6.09 (brs, 1H; NH), 4.04 (s, 2H; CH₂), 2.87 (hept, *J* = 6.9 Hz, 1H; CH), 1.19 (d, *J* = 6.9 Hz, 6H; 2CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 170.5, 157.8, 149.7, 129.2, 127.7, 126.5, 46.8, 34.3, 24.6; MS (EI): *m/z* (%): 218 (62) [*M*⁺], 203 (100), 146 (52), 69 (35); HR-MS (EI): calcd for C₁₂H₁₄O₂N [*M*⁺] 218.1055, found: 218.1057.

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- Copper leakage was not observed even in the presence of an excess of TMEDA and over the times required for a complete release (<8 h).

¹H High-Resolution Magic Angle Spinning NMR Spectroscopy for the Investigation of a Ras Lipopeptide in a Lipid Membrane**

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Membrane association is a major prerequisite for biological function of different proteins involved in cell signaling such as trimeric G proteins or the oncogen *Ras*. A salient feature of these proteins is that membrane affinity and binding is achieved by co- or posttranslational lipidation of amino acids located near the N or C terminus of the protein.^[1] Covalent attachment of myristic or palmitic acid and prenyl chains equip proteins with a hydrophobic membrane anchor directing them towards the cell membrane.

Currently, structural data on membrane-bound lipid-modified peptides are not available mostly because of missing synthesis pathways for lipidated model compounds and the failure of standard techniques for structural investigations such as X-ray crystallography and solution NMR spectroscopy to resolve structural information in the membrane environment. Recently, however, lipid-modified peptides were synthesized.^[2] These peptides not only provide excellent model systems for structural studies but also a new efficient route to lipid-modified proteins, which show activity almost as high as that of the wildtype protein.^[3]

For soluble peptides, ¹H NMR spectroscopy is a standard method to obtain high-resolution molecular structures. However, this method fails for membrane-bound peptides because these molecules do not undergo fast isotropic tumbling on the NMR time scale. Consequently, ¹H NMR lines are homogeneously broadened (typically by several kHz) due to strong anisotropic ¹H–¹H dipolar couplings, resulting in broad featureless line shapes.

For pure lipid membranes, solution-like ¹H NMR spectra can be obtained if the sample is spun about an axis oriented at 54.7° with respect to the external magnetic field (the “magic angle”; magic angle spinning, MAS). Significant resolution enhancement is achieved even at spinning speeds not exceeding the effective dipolar couplings due to fast axially symmetric motions of the lipids in the membrane.^[4] Membrane-bound peptides, however, undergo only slow motions

that broaden NMR lines and restrict spectral resolution. Recent ¹H high-resolution magic angle spinning (HR MAS) NMR investigations on membrane-bound peptides at very high spinning speeds (ca. 15 kHz) have partially overcome these limitations.^[4b, 5] Nevertheless, according to Davis et al. “to observe the high-resolution ¹H NMR spectra of either peptides or lipids in an ordered system such as a model or biological membrane, it is absolutely necessary to have rapid axially symmetric molecular reorientation”.^[4b]

Herein we present a ¹H HR MAS NMR study of a lipid-modified, membrane-bound heptapeptide, which models the C terminus of the human N-Ras protein. This method allows for the first time structural investigations of a lipid-modified, membrane-bound peptide. Membrane binding is achieved through a covalently bound palmitic fatty acid chain and a hexadecyl thioether, which are built into the membrane. This binding motif provides the peptide with motional freedom to perform axially symmetric reorientations in the bilayer, which improve the NMR line widths significantly. The amino acid sequence of the peptide investigated is H-Gly-Cys(Pal)-Met-Gly-Leu-Pro-Cys(HD)-OMe (Pal: palmitic acid, HD: hexadecyl). The peptide was incorporated into deuterated 1,2-dimyristol-*sn*-glycero-3-phosphocholine ([D₆₇]DMPC) multilamellar vesicles and investigated by ¹H HR MAS NMR spectroscopy.

Figure 1 displays the ¹H MAS NMR spectrum of the lipid/peptide dispersion. Besides the strong water peak at $\delta = 4.55$ the spectrum shows very intense signals from the fatty acid chains of the peptide as well as glycerol groups of the phospholipid due to incomplete deuteration of [D₆₇]DMPC.^[6] Typical line widths of these phospholipid signals are 0.05–0.06 ppm (approximately 30 Hz on the 600 MHz instrument). Furthermore, a large number of aliphatic peptide signals are well-resolved. The line width for these side chain signals is

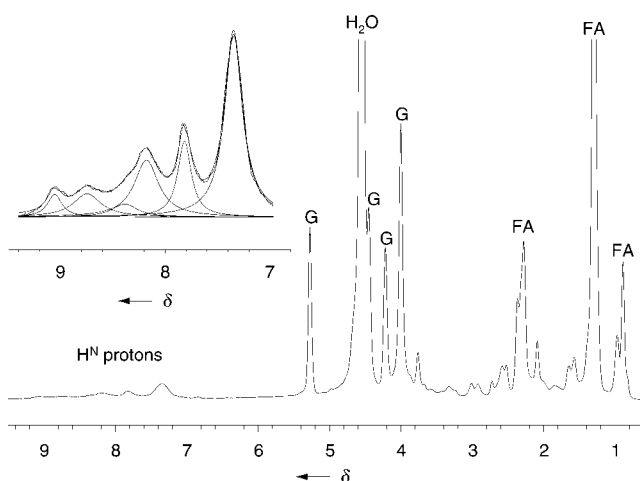


Figure 1. ¹H HR MAS NMR spectrum of the Ras peptide in [D₆₇]DMPC multilamellar liposomes (30 wt % H₂O) at a spinning speed of 12 kHz and a temperature of 37 °C. Peaks labeled with G represent glycerol signals of the phospholipid, which are not ²H labeled in [D₆₇]DMPC.^[6] Fatty acid signals (FA) of the peptide acyl chains and a large number of well-resolved aliphatic peptide signals are observed in the upfield region of the spectrum. The inset shows the amide region of the spectrum; the line shape of the amide signals could be fit with six Lorentzian lines.

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only slightly broader than those for the lipids (0.07–0.1 ppm). In the downfield region of the spectrum, the six amide protons of the peptide are resolved (proline has no amide proton). This spectral region could be fit by using six Lorentzian lines with a line width of between 0.16 and 0.32 ppm (see inset of Figure 1). The H^N proton signals are broadened by solvent exchange and scalar relaxation with the neighboring ^{14}N nuclei. The peptide backbone also represents the most rigid region of the peptide, and line broadening due to residual dipolar couplings is particularly effective. The intensity differences observed for the H^N signals could be due to the varying mobility of the amide bonds in the peptide backbone, as more mobile structures have more centerband and less sideband intensity because of weaker effective dipolar couplings. In contrast, more rigid structures exhibit stronger dipolar couplings and, consequently, more sideband and less centerband intensity.^[6]

Increased resolution and long spin-lattice relaxation times allow acquisition of 2D nuclear Overhauser enhancement spectra (NOESY). In this way magnetization exchange of protons can be probed up to distances of 5 Å.^[7] For HR MAS studies, the same NOESY pulse sequence as used in high-resolution NMR spectroscopy is applied. Magnetization transfer is monitored by the appearance of a non-diagonal cross-peak in the 2D NOESY spectrum. Figure 2 shows the

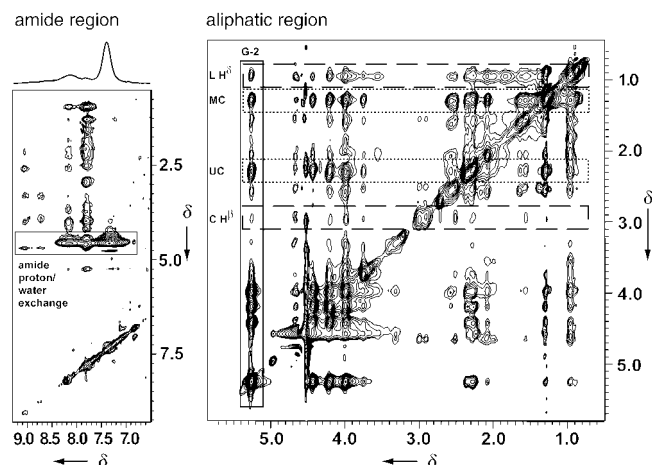


Figure 2. ^1H HR MAS NOESY spectrum of the Ras peptide in a $[D_{67}]$ DMPC multilamellar liposomes at a mixing time of 200 ms. The aliphatic region shows cross-peaks of the glycerol (G-2) signal with various peptide and lipid signals (solid box). Dashed boxes emphasize cross-peaks for the β protons of the Cys residues (CH^β) and the δ protons of the leucine residue (LH^δ), respectively. Cross-peaks of the upper (UC) and middle (MC) peptide's acyl chains are shown in the dotted box. In the amide proton region cross-peaks due to exchange of labile protons with the solvent are highlighted. A section of the 2D spectrum taken at the shift of the water signal ($\delta = 4.55$) is also displayed, which confirms that all amide protons participate in the exchange with water.

aliphatic and H^N region of the ^1H HR MAS NOESY spectrum at a mixing time of 200 ms. Typically, three types of cross-peaks are observed. a) Intramolecular cross-peaks due to magnetization transfer within the peptide. This magnetization transfer is modulated by the overall motion of the molecule on the membrane surface and can be converted into proton–proton distance constraints for structure calculations. b) In-

termolecular cross-relaxation between lipid and peptide is modulated by variations of the internuclear distance vector through motions of the entire molecules. Since intermolecular distances vary significantly in liquid crystals, these cross-relaxation rates cannot be converted into fixed molecular distances but rather represent the contact probability between molecular segments^[6, 8] and are used for their location in the membrane.^[9] c) Chemical exchange between labile H^N protons and water gives rise to cross-peaks that provide information on the water accessibility of amino acids in the membrane.^[10]

In the NOESY spectra of membrane-bound Ras peptides all three types of cross-peaks are observed. It is beyond the scope of this communication to provide a full assignment and discussion of all occurring cross-peaks; however, a few interesting correlations are highlighted. Our tentative assignment of the signals is based on the assignment of the signals of the peptide in $CDCl_3$.^[2] For instance, the H^δ protons of Leu at $\delta = 0.95$, show very strong cross-peaks with the glycerol and the upper chain region of the phospholipids. Similarly, the H^β protons of the two Cys residues ($\delta = 3.01$ and $\delta = 2.92$) show cross-peaks with glycerol and upper chain signals of the lipids; however, no contacts between the Cys- H^β protons and the methylene or methyl segments of the peptide acyl chains are observed. This suggests that the location of Leu and Cys side chains is in the glycerol and upper acyl chain region of the membrane. This is consistent with the assumption that insertion of the peptide's lipid chains in the membrane drag the Cys side chains deeper into the nonpolar lipid region of the membrane, allowing favorable interactions with upper acyl chain segments. According to the experimental hydrophobicity scale developed by Wimley and White^[11] the total free energy of transferring the peptide from the aqueous phase to the membrane is $-0.8 \text{ kcal mol}^{-1}$, indicating the high propensity of the Ras peptide for the membrane even in the absence of lipid modification.

To further probe the location of the peptide in the lipid bilayer the exchange of labile amide protons with water was analyzed. In the H^N region of the NOESY spectrum, intramolecular cross-peaks between amide protons and peptide side chains are observed as well as intermolecular cross-peaks with glycerol and acyl chain signals (Figure 2). In addition, the spectrum shows three strong cross-peaks due to the chemical exchange of H^N protons with H_2O , whereas the other amide protons show weak exchange cross-peaks. By evaluating the section of the 2D spectrum at $\delta = 4.55$, it can be verified that all H^N protons participate in the exchange with water. In contrast, amide protons, which are buried in the hydrophobic core of the membrane, are protected from water exchange, whereas amino acids located in the lipid/water interface are exchangeable.^[12] For the Ras peptide, all amide protons participate in the water exchange, suggesting the location of the peptide backbone is in the water-accessible part of the membrane, that is in the lipid/water interface defined by the headgroup, the glycerol units, and the upper chain region.^[13]

In summary, we have shown that the ^1H HR MAS NMR spectra of a membrane-bound lipopeptide provide excellent spectral resolution for the structural investigation of these model systems. The Ras peptide was located in the lipid/water

interface of the membrane, while the peptide acyl chains are inserted into the interior of the membrane (Figure 3). The lipid/water interface of the membrane represents a broad zone containing disordered headgroups, glycerol, and upper chain segments, which is easily accessed by water molecules.^[13]

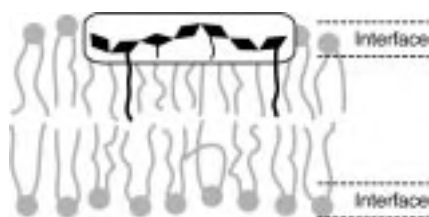


Figure 3. Schematic representation of the location of the Ras peptide in the lipid/water interface of the membrane (headgroup, glycerol, and upper chain region). The peptide acyl chains and hydrophobic side chains extend deeper into the hydrophobic part of the membrane.

The hydrophobic peptide side chains project into the acyl chain region of the membrane, where the low polarity environment allows favorable hydrophobic interactions with the lipid chains. The polar backbone of the peptide interacts strongly with the aqueous phase. For the peptide/lipid system investigated here a full assignment of the NMR signals as well as a quantitative analysis of the location and membrane-bound structure of the peptide appears to be feasible by using HR MAS NMR spectroscopy, thus providing more insight into this important mechanism for membrane binding and protein insertion.

Experimental Section

[D₆₇]1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine ([D₆₇]DMPC) was used without purification. The lipid-modified N-Ras peptide was synthesized enzymatically as described before.^[2] For the preparation of the NMR samples, phospholipid and peptide (molar ratio of 10:1) were combined in methanol, dried under a stream of nitrogen, dissolved in cyclohexane and lyophilized. The samples were hydrated to 30 wt % H₂O, freeze-thawed, stirred, and gently centrifuged for equilibration and transferred into spherical inserts for 4-mm MAS rotors. NMR experiments were carried out on a Bruker DRX600 spectrometer at a resonance frequency of 600.13 MHz at 37 °C. The MAS frequency was 12 kHz. Spectra were acquired at a spectral width of 10.9 kHz with a 90° pulse length of 6.2 μs. For phase-sensitive NOESY experiments (mixing time 200 ms) 400 complex data points were collected in the indirect dimensions with 32 scans per increment with a 4 s relaxation delay between successive scans.

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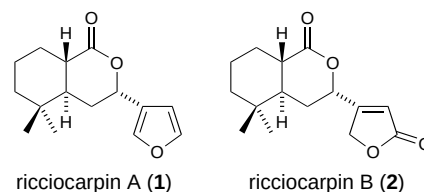
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Enantioselective Synthesis of the Ricciocarpins A and B**

Christoph Held, Roland Fröhlich, and Peter Metz*

Dedicated to Professor Wittko Francke on the occasion of his 60th birthday

The furanosesquiterpene lactone ricciocarpin A (**1**) isolated from the liverwort *Ricciocarpos natans* exhibits high molluscicidal activity against the water snail *Biomphalaria glabrata*, one of the vectors of schistosomiasis (bilharziasis).^[1] Though several syntheses were published for racemic **1**,^[2]

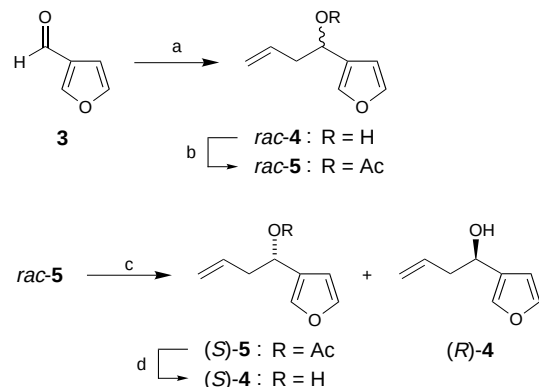


no enantioselective version has so far been reported. Since the absolute configuration of **1** was unknown prior to our work, we principally wanted to devise an access to both enantiomers. Moreover, we were also interested in developing a first synthetic access to the structurally similar liverwort-constituent ricciocarpin B (**2**).^[1] Our synthesis of **1** reported here relies heavily on the twofold application of the catalytic ring-closing metathesis (RCM)^[3] to generate both six-membered rings of the target.

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Furan-3-carbaldehyde (**3**), which has already been converted into both enantiomers of the homoallylic alcohol **4** by stoichiometric asymmetric allylboration, was used as the starting material^[4] (Scheme 1). We investigated different

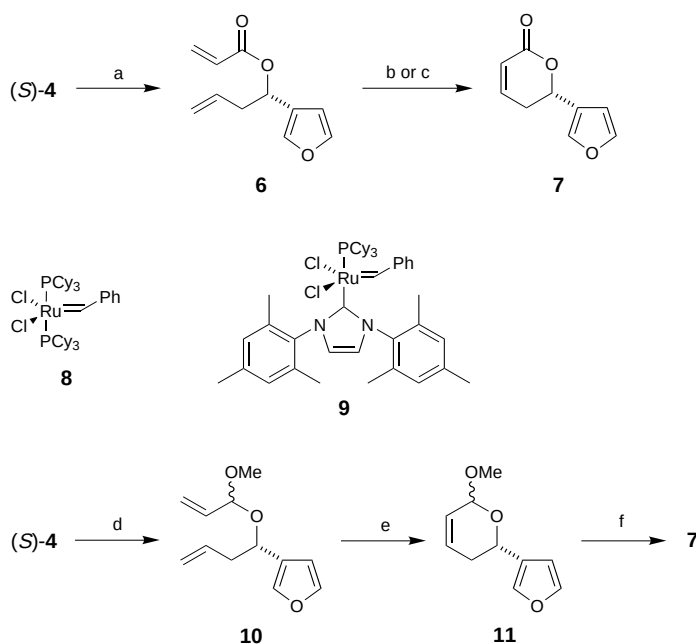


Scheme 1. a) Zn, CH₂=CHCH₂Br, NH₄Cl/H₂O/THF, 25 °C, 95%; b) Ac₂O, NEt₃, DMAP, CH₂Cl₂, 25 °C, 95%; c) lipase from *Alcaligines sp.*, H₂O/DMSO (10:1), pH 7, 25 °C, 44% (S)-5 (99% ee), 48% (R)-4 (88% ee); d) NaOH, 25 °C, 97% (99% ee). Ac = acetyl, DMAP = 4-dimethylaminopyridine.

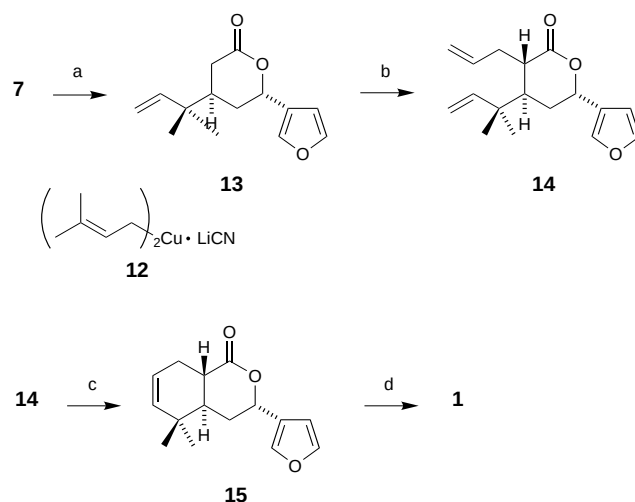
procedures for the enzymatic kinetic resolution of *rac*-4 as well as of the derived acetate *rac*-5 using commercially available esterases and lipases.^[5] For the preparation of *rac*-4, aldehyde **3** was subjected to a Barbier reaction with allyl bromide and zinc.^[6] Hydrolysis of *rac*-5 catalyzed by a lipase from *Alcaligines sp.* gave the best results. In addition to (R)-4 (88% ee by GC), this protocol provided (S)-5 (99% ee by GC), which was transformed to (S)-4 by alkaline hydrolysis after chromatographic separation from (R)-4. Thus, both enantiomers of **4** were at hand in high enantiomeric purity by asymmetric catalysis.

Alcohol (S)-4 was converted into the acrylate **6** with acryloyl chloride (Scheme 2). Application of a reagent system^[7] consisting of Grubbs' catalyst **8** and titanium tetraisopropoxide in the molar ratio 1/3 led to a 65% yield of **7** when a relatively high catalyst loading was used. In the presence of 5 mol % of catalyst **9**, which exhibits an enhanced reactivity towards acrylates,^[8] lactone **7** was obtained in 68% yield. Transition to the less Lewis basic mixed acetal **10** promised a further improvement in the yield of the metathesis. Compound **10** was prepared in good yield by a palladium-catalyzed reaction of (S)-4 with methoxyallene.^[9] Use of the standard conditions for the RCM (5 mol % **8**, CH₂Cl₂, 25 °C, 2 h) resulted in a 98% yield of acetal **11**. The high reaction rate allowed a reduction in the amount of catalyst **8** to only 0.75 mol % while maintaining a nearly equally high yield (95%) of **11**. By omitting the solvent the reaction could be run at reduced pressure, which guaranteed an efficient removal of the ethene produced during the metathesis. A chemoselective oxidation^[10] of acetal **11** to the unsaturated lactone **7** completed the alternative route to this crucial intermediate.

Lactone **7** was transformed to diene **14** through two allylation reactions (Scheme 3). First, a conjugate addition of cuprate **12**^[11] to give lactone **13** took place with complete regio- and stereoselectivity, as monitored by capillary GC



Scheme 2. a) CH₂=CHCOCl, NEt₃, DMAP, CH₂Cl₂, 0 → 25 °C, 80%; b) 10 mol % **8**, 30 mol % Ti(O^{*i*}Pr)₄, CH₂Cl₂, 40 °C, 65%; c) 5 mol % **9**, CH₂Cl₂, 40 °C, 68%; d) CH₂=C=CHOMe, 5 mol % Pd(OAc)₂/dppp, NEt₃, CH₃CN, reflux, 80%; e) 0.75 mol % **8**, 0.5 mbar, 25 °C, 95%; f) MoO₃, H₂O₂/THF, -5 → 25 °C, then Ac₂O, NEt₃, CH₂Cl₂, 0 → 25 °C, 75%. Cy = cyclohexyl, dppp = 1,3-bis(diphenylphosphanyl)propane.

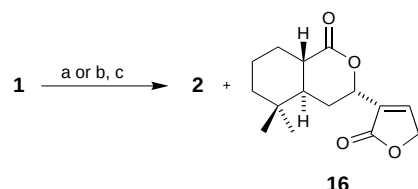


Scheme 3. a) **12**, THF, -78 °C, then NH₄Cl/H₂O, -78 → 25 °C, 65%; b) LDA, THF, -78 °C, then CH₂=CHCH₂Br, -78 → 25 °C, 80%; c) 1.5 mol % **8**, CH₂Cl₂, 25 °C, 97%; d) 1 atm H₂, 10 mol % [RhCl(PPh₃)₃], benzene, 25 °C, 97%. LDA = lithium diisopropylamide.

analysis. The subsequent α -allylation, which yielded the substrate **14** for the second ring-closing metathesis, occurred only *trans* to the bulky dimethylallyl group. Again, no additional isomer could be detected by capillary GC. Diene **14** was subjected to an RCM under standard conditions, whereupon the cyclohexene **15** was isolated in high yield.^[12] Since no reaction was observed between 3,3-dimethylbut-1-ene and **8** under similar conditions^[13] the smooth conversion noted in our case is surely primarily a consequence of the intramolecular mode of attack on the sterically hindered olefin. Finally, homogeneous catalytic hydrogenation of

cyclohexene **15** led to (3*S*,4*aR*,8*aS*)-**1**, which proved to be identical (by comparison of optical rotation data) to the naturally occurring enantiomer of ricciocarpin A.^[14] Hence we have developed a short, highly enantioselective and completely diastereoselective route to ricciocarpin A.

As ricciocarpin B (**2**) only differs from **1** within the five-membered ring, we tried to convert **1** into **2** by oxidation (Scheme 4). The bislactones **2** and **16** were obtained after



Scheme 4. a) 1 atm O₂, methylene blue, *hν*, MeOH, −40 °C, then 25 °C; b) 1 atm O₂, methylene blue, DIPEA, *hν*, CH₂Cl₂, −78 °C, then 25 °C; c) NaBH₄, MeOH, 25 °C, 25 % **2**, and 25 % **16** from **1** by steps (a) and (c), 46 % **2** by steps (b) and (c). DIPEA = diisopropylethylamine.

[4+2] cycloaddition with singlet oxygen and subsequent thermal decomposition of the primary adduct as well as reduction with sodium borohydride.^[15, 16] By comparison of the analytical data with literature values^[11a] **2** could be identified as ricciocarpin B.^[17] To the best of our knowledge the transformation of **1** to **2** reported here constitutes the first synthesis of ricciocarpin B. A crystal structure analysis of **16** was accomplished, and the depicted absolute configuration was proven by anomalous X-ray diffraction.^[18] Thus, this analysis also secures the configurational assignment for **4**, which so far relied on analogy to the outcome of related allylboration^[4] or on observations that some hydrolases preferentially attack a certain enantiomer in a substrate-independent fashion.^[5, 19] The formation of **16** could be completely suppressed by photooxygenation in the presence of a sterically demanding base,^[20] and the yield of **2** raised to 46 % (non-optimized).

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- [18] Crystal dimensions 0.40 × 0.40 × 0.20 mm³, monoclinic, space group *P*2₁ (No. 4), *a* = 8.194(1), *b* = 8.747(1), *c* = 10.251(1) Å, β = 112.81°, *V* = 677.3(1) Å³, ρ_{calcd} = 1.296 g cm^{−3}, 2θ_{max} = 148.4°, CuKα radiation, λ = 1.54178 Å, 9/2θ scans, *T* = 223 K, 2813 reflections measured, 2525 independent (*R*_{int} = 0.021), of which 2495 were observed [*I* ≥ 2σ(*I*)], μ = 7.61 cm^{−1}, absorption correction by ψ-scan data (min/max transmission 0.751/0.863), structure solution by direct methods, 175 refined parameters, hydrogen atoms were calculated and refined as riding atoms, *R* = 0.030, *wR*² = 0.085, max/min residual electron density 0.18/−0.13 e Å^{−3}, Flack parameter −0.06(16). Programs used: Express, MolEN, SHELXS-97, SHELXL-97, and SCHAKAL. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-150983. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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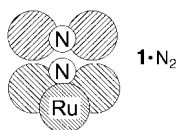
The Ammonia-Synthesis Catalyst of the Next Generation: Barium-Promoted Oxide-Supported Ruthenium

Hubert Bielawa, Olaf Hinrichsen, Alexander Birkner, and Martin Muhler*

Ammonia synthesis is one of the largest energy-consuming processes of the industrialized world requiring approximately 1% of the world's power production. Hence, searching for new and more efficient processes for ammonia synthesis is one of the important targets of chemical technology. Even in the early investigations carried out by Mittasch, which resulted in the industrially used multipromoted iron catalyst, ruthenium was tested as an active component.^[1] Ruthenium was found to have the highest catalytic activity after osmium and iron. In the field of ruthenium catalysts the pioneering work was carried out by the Japanese group led by Aika. During the last three decades they prepared a huge number of different ruthenium catalysts containing various promoters and supports which were then investigated by means of a standardized screening procedure.^[2]

Work carried out by Tennison and co-workers at British Petroleum (BP) finally led to a ruthenium catalyst of commercial interest. It consists of ruthenium on a specially pretreated carbon support (high surface area graphite, HSAG). The high catalytic activity was achieved by copromoting with cesium and barium.^[3] This catalyst is used industrially in the low-energy, low-pressure ammonia synthesis process of Kellogg Brown & Root (KBR Advanced Ammonia Process, KAAP). Since 1998 the two largest plants world-wide for ammonia synthesis are operating in Trinidad with a capacity of 1850 tons of NH₃ per day, each employs the iron catalyst (in the first fixed bed) and the ruthenium catalyst (second to fourth fixed bed) in a multitubed reactor.^[4] However, the application of carbon-supported ruthenium catalysts is not without problems. The susceptibility of the support to methanization was drastically lowered by a special pretreatment but could not be completely eliminated.^[5]

Recently, the question as to what is the active site on ruthenium catalysts was clarified. The Danish group led by Chorkendorff showed that the so-called B₅-type site **1** is responsible for the activity of ruthenium catalysts. The B₅-type site **1** consists of an arrangement of three ruthenium atoms in one layer and two further ruthenium atoms in the layer directly above this at a monoatomic step on an Ru(0001) terrace.^[6] For the unpromoted ruthenium catalyst a simple geometric model, established by van Hardeveld and van



Montfoort for nickel crystallites,^[7] can be used to calculate the optimum size of the ruthenium particles, about 2 nm, to give the maximum number of B₅-type sites.^[6] Our studies showed that the B₅-type sites also dominate the activity of promoted ruthenium catalysts (see Table 2).^[8]

Herein we first present a solvent-free preparation method of supported ruthenium catalysts. Table 1 compares the

Table 1. Characterization of two Ru/MgO catalysts prepared either by impregnation or by MOCVD.

	Impregnation	MOCVD
Specific surface area (BET) [m ² g ⁻¹]	56	51
Specific Ru surface area ^[a] [m ² g ⁻¹]	12.2	12.2
Ru content (ICP-OES analysis) [wt %]	3.3	3.4
Dispersion ^[a] [%]	75	73
Ru particle size ^[b] [nm]	1.3	1.4
Production rate ^[c] [mmol NH ₃ g ⁻¹ h ⁻¹]	0.35	0.37

[a] Measured by static H₂ chemisorption. [b] Assuming spherical particles. [c] T = 588 K, p = 0.1 MPa.

results obtained with a catalyst prepared conventionally (by impregnation) with those of a catalyst manufactured in a solvent-free route. It is clearly evident that these two procedures lead to almost identical catalysts. The solvent-free way of preparation is based on the MOCVD technique (chemical vapor deposition of organometallic compounds) which decreases the number of necessary unit operations, avoids solvent effects, and has a significantly higher reproducibility. In Equation (1) a power-law rate expression is given

$$r = k p_{\text{NH}_3}^\alpha p_{\text{N}_2}^\beta p_{\text{H}_2}^\gamma \quad (1)$$

which is often used in chemical reaction engineering for the design of industrial reactors. A kinetic investigation based on this expression gave within the experimental accuracy limits (reaction orders: ±0.1, activation energies: ±2 kJ mol⁻¹) identical parameters for the catalysts prepared in both ways (Table 2) thus confirming their similarity.

Table 2. Comparison of the reaction orders of the Ru/MgO catalysts and the Ba-Ru/MgO catalyst.

Catalyst	p [MPa]	T [K]	α(NH ₃)	β(N ₂)	γ(H ₂)	E _a [kJ mol ⁻¹]
Ru/MgO (impreg)	0.1	543–623	–0.5	0.9	–0.4	74
Ru/MgO (MOCVD)	0.1	543–643	–0.6	0.8	–0.5	76
Ru/MgO (MOCVD)	2	588–673	–0.6	0.8	–0.7	79
Ba-Ru/MgO	2	513–588	–0.6	0.8	–0.6	77

Catalytic measurements with various samples showed that both preparation methods lead to catalysts with activities between the maximum described by trace d (Figure 1) and the minimum described by curve e in Figure 1. These unpromoted, oxide-supported ruthenium catalysts are less active than the industrially used multipromoted iron catalyst (trace c). In contrast, cesium-promoted ruthenium catalysts display an activity many times higher than that of the industrial iron catalyst (trace b). The activity at 588 K is three to four times higher than that of the iron catalyst.^[9] Promoting oxide-supported ruthenium catalysts with barium resulted in

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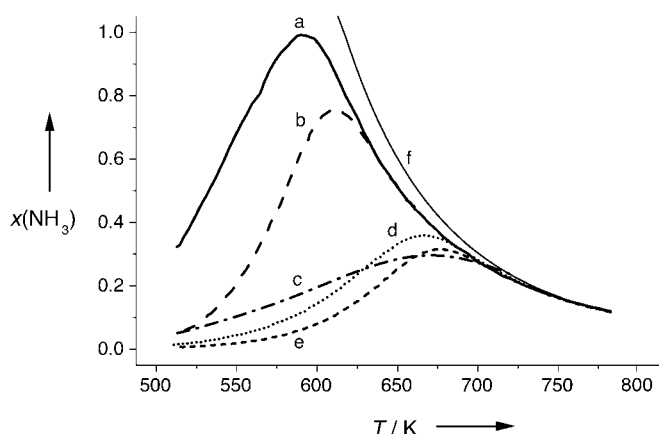


Figure 1. Catalytic activity of a) the barium-promoted catalyst (Ba-Ru/MgO), b) the cesium-promoted catalyst (Cs-Ru/MgO), c) the industrial iron catalyst, d, e) unpromoted Ru/MgO catalysts (Ru/MgO), and f) values of ammonia mole fractions at equilibrium are shown. Measurements were performed using a mixture of $p_{N_2}:p_{H_2} = 1:3$ ($Q = 40 \text{ mL min}^{-1}$ (STP), $p = 0.1 \text{ MPa}$) at quasi-stationary conditions while decreasing the catalyst-bed temperature (2 K min^{-1}). All measurements were conducted in our micro-reactor set-up using the same conditions. $x(\text{NH}_3)$ is given in %.

catalysts (trace a) with the highest activity of all the catalysts reported so far including the commercial ruthenium/carbon catalyst.^[3, 8] The activity of the barium-promoted catalyst in the kinetically controlled regime up to approximately 600 K is an order of magnitude higher than that of the iron catalyst. This sequence of activity remains unchanged even at high pressures. Barium-promoted catalysts lead to more than double the yield of NH_3 compared with a cesium-promoted catalyst under roughly the same high-pressure conditions (Table 3). To reach such a high yield with the industrial iron catalyst, a pressure of 10.7 MPa instead of 5 MPa (for the Ba-Ru/MgO system) and higher temperatures would be necessary. The generation of such high pressures is a key part of the energy demand in the conventional ammonia synthesis process.

Table 3. Comparison of high-pressure activity of Ru/MgO, Cs-Ru/MgO, Ba-Ru/MgO, and the industrial multiply promoted iron catalyst. Results are expressed as NH_3 mole fraction in the effluent using a GHSV (gas hourly space velocity) of about 16000 h^{-1} .

	T [K]	p [MPa]	GHSV [h^{-1}]	Q [mL min^{-1} (STP)]	$x(\text{NH}_3)$
Ru/MgO	783	5	13 900	40	5.04
Cs-Ru/MgO	665	5	13 900	40	5.90
Ba-Ru/MgO	684	5	16 100	40	12.8
Iron ^[a]	723	10.7	16 000	305	13.2

[a] Data taken from ref. [10].

Figure 2 indicates the lengthy activation procedure and the dependence of the catalytic activity on the reduction temperature for the barium-promoted catalyst. During the activity measurement the reduction of the catalyst took place by increasing the catalyst-bed temperature in a flow of synthesis gas. The maximum temperature during an activity measurement thus corresponds to the maximum reduction temperature. After approximately 45 h steady state was still not achieved (upper part of Figure 2). By increasing the maximum

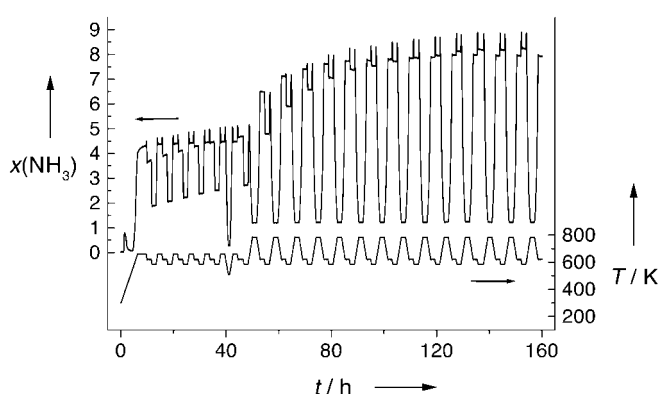


Figure 2. Activation of the barium-promoted catalyst as a function of temperature and time. Conditions: $p_{N_2}:p_{H_2} = 1:3$, $Q = 40 \text{ mL min}^{-1}$ (STP), $p = 0.1 \text{ MPa}$. $x(\text{NH}_3)$ as a function of time (top curve) is given in 10^3 ppm ; the bottom curve shows the temperature change with time.

temperature from 663 to 783 K after about 50 h (lower part of Figure 2) the catalytic activity almost doubled at the measurement temperature of 588 K and continued to rise during the measurement. Finally, after more than 120 h a constant catalytic activity was achieved. This example clearly demonstrates the limits of conventional fast-screening methods used, for example, by Aika et al; they would have found only a moderate activity of the Ba-Ru/MgO-catalyst.^[11] In spite of a large number of experiments in the field of supported Ru catalysts during the last 30 years, Aika et al. did not discover the most active catalyst because of the fast and not sufficiently thorough testing method. The same risk is inherent to highly developed throughput methods in which the time on stream can be less than one minute per sample.^[12] However, if the catalyst screening is accelerated by using several reactors connected in parallel, then the risk of wrong assessment of catalysts requiring long activation periods is minimized.

Aika and co-workers also investigated the influence of the reduction temperature and of the Ba:Ru ratio of the MgO-supported ruthenium catalyst. They observed a decrease in catalytic activity for reduction temperatures above 573 K in disagreement with our results.^[11] Our investigations showed an increasing rate of ammonia production and an increase in metal surface area at reduction temperatures up to 783 K. Further investigations of the influence of the reduction temperature beyond 783 K revealed a decrease in metal surface area although the catalytic activity still increased.^[8] This indicates particle growth up to an optimum particle size which, in turn, is determined by the maximum number of B_5 -type sites.^[6-8] The identical reaction orders within the experimental accuracy limits (Table 2) of the barium-promoted Ru catalyst and of the unpromoted Ru/MgO catalyst indicate the same active sites for both catalysts.^[6, 8] Clearly, the Ba+O coadsorbate is able to induce a reconstruction of the Ru surfaces, whereby the number of the B_5 -type sites is increased. Figure 3 shows a transmission electron microscopy (TEM) micrograph of the Ba-Ru/MgO catalyst after reduction at 783 K revealing the presence of very small Ru particles, approximately 2 nm in size. This value is in good agreement with the average particle size of 1.3 nm derived from static chemisorption measurements. The high dispersion (76 %), the

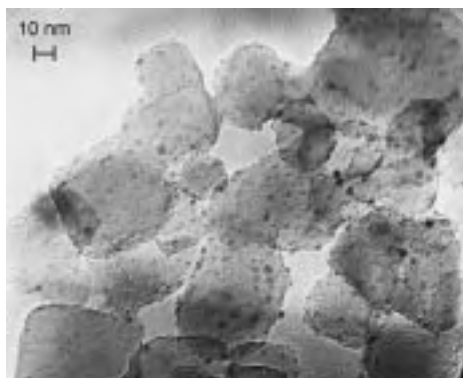


Figure 3. TEM image of the Ba-Ru/MgO catalyst after reduction at 783 K.

evenly distributed Ru particles on the cubic MgO particles, and the narrow particle-size distribution demonstrate the high quality of the MOCVD preparation.

Our knowledge-based approach, leading to the Ba-Ru/MgO catalyst relies on a combination of kinetic and spectroscopic techniques including results from single-crystal surfaces, contrasts with the “trial and error” method. The latter method was used by Mittasch who tested more than 3000 catalyst compositions in over 20 000 experiments at the beginning of the last century,^[1] and it is also used today in combinatorial chemistry.^[12] Our barium-promoted Ru/MgO catalyst also displays a high long-term stability. Correspondingly, the high catalytic activity remained constant after more than 1000 hours on stream at a pressure of 5 MPa and temperatures up to 1023 K.^[8] Because of this high stability and the very high catalytic activity the Ba-Ru/MgO catalyst can be considered as an alternative, not only to the iron catalyst, but also to the industrially used multipromoted Ru/C catalyst, the long-term stability of which is limited by the inevitable methanization of the carbon support. Furthermore, the Ba-Ru/MgO catalyst offers the advantage that the components are completely recyclable. The components can be separated and reclaimed with high purity (promoter > 97%, ruthenium > 94%, support) by a simple three-stage process.^[13]

The yield of ammonia can be further increased by a knowledge-based optimization of the Ba-Ru/MgO catalyst with respect to the ruthenium loading, the properties of the support, and the synthesis process conditions (ratio of N₂ to H₂ etc.). In this way, an additional increase of the ammonia production rate can be achieved far exceeding that of the Ru/C catalyst that is considered an alternative to the industrially used iron catalyst. Consequently, the barium-promoted ruthenium catalyst supported on oxides represents the ammonia-synthesis catalyst of the next generation.

Experimental Section

Typically, an unpromoted Ru/MgO catalyst with 5 wt% ruthenium was prepared from MgO (2 g, Johnson Matthey) and [Ru₃(CO)₁₂] (0.222 g, Strem) by mixing in an agate mortar for 0.5 h. The completely homogeneous precursor mixture was pressed into tablets then crushed and sieved to obtain a particle size fraction of 250–355 µm. Afterwards the precursor was thermally decomposed in a quartz ampoule on a vacuum line equipped with a turbomolecular pump under high vacuum conditions by executing a multistage temperature program (2 K min⁻¹ up to 313 K, hold for 1 h; in 2 h up to 343 K, hold for 1 h; in 2 h up to 393 K, hold for 1 h; in 5 h up to 723 K,

hold for 2 h; cooling down to ambient temperature). The decomposed precursor was reduced in situ in the microreactor flow set-up at 1 bar in a stream of synthesis gas while the temperature was increased to 723 K at 1 K min⁻¹. The preparation by impregnation is described in a previous publication.^[9]

To obtain the precursor of the barium-promoted ruthenium catalyst in the molar ratio of Ba:Ru = 1:1 the thermally decomposed, unreduced precursor (1 g) was stirred in a solution of Ba(NO₃)₂ (0.129 g) and solvent (H₂O:EtOH = 50:50; 60 mL) for 4 h. Subsequently, the solvent was removed on a rotary evaporator at 363 K and 10 kPa. The promoted precursor was dried at 363 K in vacuum by using a diaphragm pump (final pressure: 1 kPa) and reduced in the flow set-up. The temperature program used for the activation of the promoted ruthenium catalyst was very important (see Figure 2).

The catalytic activity of the catalysts was determined in a high-pressure microreactor flow set-up which was equipped with two fixed-bed reactors, two independent gas supplies, and two NH₃ detector channels (NH₃ infrared detector BINOS, Fisher Rosemount). This set-up allows parallel catalyst screening to be performed. Accordingly, while the activity of one catalyst was measured another catalyst was activated. This arrangement was necessary because of the lengthy activation procedure of the catalysts (see Figure 2).

The H₂ chemisorption measurements were used to derive the specific surface area, the dispersion, and the particle size of ruthenium. For this purpose the catalyst samples were reduced in an Autosorb 1C unit supplied by Quantachrome. The TEM micrograph of the Ba-Ru/MgO after synthesis was obtained with a Hitachi H 8100 microscope.

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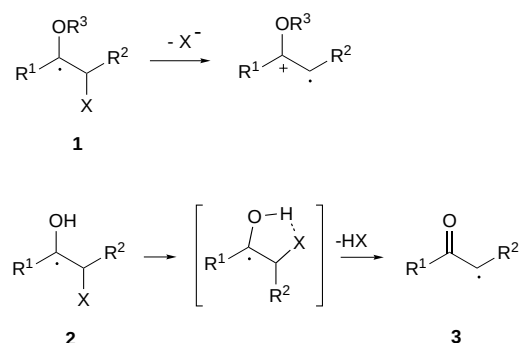
A New Photochemical Route to Cyclopropanes**

Pablo Wessig* and Olaf Mühling

Cyclopropanes have always fascinated organic chemists. Due to their considerable ring strain they are very versatile synthetic building blocks and many interesting applications are published every year. Furthermore, the cyclopropane ring is found in many natural products^[1] and has been used to restrict the conformational flexibility of molecules (for example, peptides^[2]). There are many valuable methods for the preparation of cyclopropanes,^[3] but nevertheless, there is still a great need for new methods. Herein, we wish to report on a new photochemical route to cyclopropanes.

The Norrish–Yang reaction, one of the best investigated photochemical reactions,^[4] was used to synthesize many homo- and heterocyclic molecules. Amongst these cyclizations the formation of cyclopropanes is conspicuous in that it was very rarely observed. Obviously, the considerable ring strain of the five-membered transition state accounts for this. In almost all cases of cyclopropane synthesis using the Norrish–Yang reaction an initial photoelectron transfer process (PET) has been proven or seems very likely.^[5]

As expected, the intramolecular hydrogen abstraction in the course of the Norrish–Yang reaction takes place preferentially at the γ -position to form 1,4-diradicals, unless this position is blocked. (For exceptions, see ref. [6].) Based on this fact we developed a method that makes use of a well-known property of monoradicals, namely that they are excellent neighbors for the displacement of leaving groups.^[7] Particularly when the radical center is stabilized by an oxygen atom elimination occurs very fast. Two cases must be distinguished that differ crucially from each other in their reaction mechanisms. While α -alkoxy radicals **1** are cleaved heterolytically to give free ions, α -hydroxy radicals **2** undergo a concerted elimination of the acid HX (Scheme 1).^[8] We



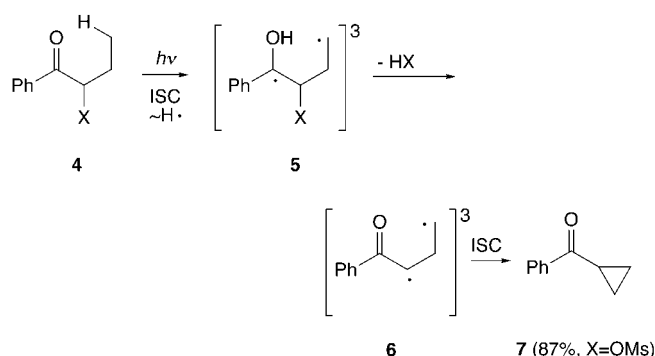
Scheme 1. Cleavage mechanisms for α -alkoxy radicals **1** and α -hydroxy radicals **2**.

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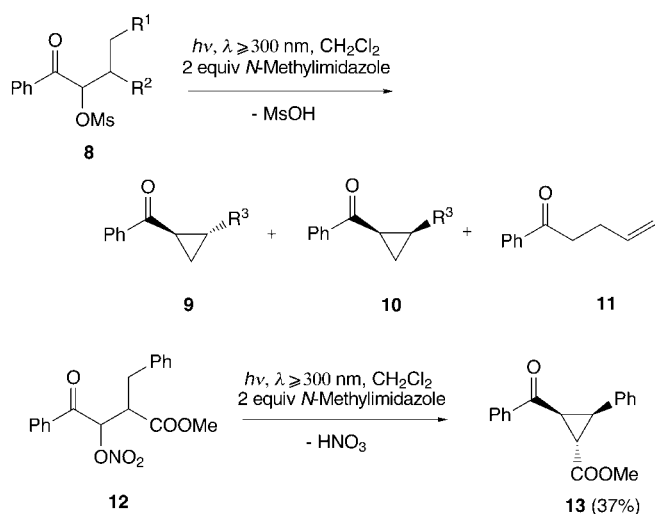
were particularly interested in the latter case because α -hydroxy radicals are intermediates in the Norrish–Yang reaction. It is noteworthy that the spin density in the formed enolate radical **3** is shifted to the adjacent atom. The question is whether the elimination of the acid HX is fast enough to proceed within the very short lifetime (approximately 10 ns) of the triplet diradicals produced in the Norrish–Yang reaction.

We first optimized the reaction conditions with the model reactant 2-X-butyrophenone **4** where X[–] represents a leaving group (Scheme 2). We found that the most suitable solvent is



Scheme 2. Photochemical behavior of 2-substituted butyrophenones **4**. ISC = intersystem crossing, Ms = mesyl = methanesulfonyl.

dichloromethane because in some other solvents, such as diethyl ether, the Norrish Type II cleavage of the triplet 1,4-diradicals **5** predominates. The leaving group X[–] must be the counterion of a strong acid. Amongst carboxylates only trifluoroacetate can be used. Sulfonates are preferable, partly due to their straightforward introduction, although in one case (**12**, see Scheme 3) we used the nitrooxy group. Naturally, the elimination **5**→**6** produces a strong sulfonic acid and we found that this acid is a serious problem in our reaction. While benzoylcyclopropane **7** by itself is stable under the irradiation conditions ($\lambda_{\text{irr}} \geq 300$ nm), the cyclopropane ring is rapidly opened if the irradiation is performed in the presence of the



Scheme 3. Photochemical behavior of di- and trisubstituted butyrophenones **8**.

acid. Therefore, the addition of an acid scavenger, which must be compatible with the photochemistry, is necessary. Amongst several tested scavengers *N*-methylimidazole proved to be most suitable. After these optimizations we obtained benzoylcyclopropane **7** with a remarkable yield of 87% (Scheme 2).

We introduced various substituents to investigate their influence on the chemo- and stereoselectivity of the cyclopropane formation. The reaction outcome substantially depends on the position of the substituents. Whereas 2-mesyloxyvalerophenone **8a** gave a mixture of the desired cyclopropane **9a** (63%) and the unsaturated ketone **11a** (16%, a product of the well-known ring opening of *cis*-1-benzoyl-2-alkylcyclopropanes;^[9] Scheme 3, Table 1), the branched isovalero-phenone **8b** provided exclusively the *trans*-1-benzoyl-2-methylcyclopropane **9b**.

Table 1. Photochemical synthesis of cyclopropanes **9** and **10**.

Reactant	R ¹	R ²	R ³	Yields [%]		
				9	10	11
8a	Me	H	Me	63	0	16
8b	H	Me	Me	90	0	0
8c	Ph	H	Ph	47	31	–
8d	H	Ph	Ph	26	18	–
8e	H	COOMe	COOMe	59	0	–
8f ^[a]	OBn	H	OBn	46	0	–

[a] Bn = benzyl.

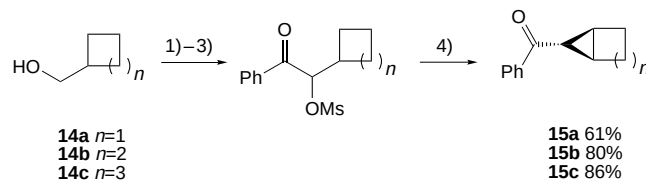
The photochemical behavior of β - and γ -phenyl-substituted butyrophenones **8c, d** was surprising at first. No matter at which position the phenyl group was placed we always obtained a 60:40 mixture of *cis*- and *trans*-1-benzoyl-2-phenylcyclopropane isomers **9c, 10c**, despite the fact that the yields differed significantly. The same product ratio was obtained by irradiation of each of the pure isomers **9c** and **10c** respectively. Obviously, aryl-substituted benzoylcyclopropanes undergo photochemical *cis*–*trans* isomerization, probably through an intramolecular charge transfer.^[10]

The stereochemical course of the cyclization of alkyl- and aryl-substituted reactants should mainly be controlled by steric interactions. In contrast to this, **8e**, which bears an ester group in β -position, gave only the *trans*-configured ketoester **9e** in good yield. A photochemical behavior similar to that of the ester **8e** is shown by the ether **8f**. Upon irradiation, only the *trans*-cyclopropane **9f** is formed. The stereoselective ring closure of **8e, f** clearly indicates the importance of dipole–dipole interactions for the stereocontrol.

The photochemical behavior of the 2,3,4-trisubstituted butyrophenone **12** (Scheme 3) illustrates the efficiency of our method. Despite the moderate yield, we obtained only one diastereomer of the trisubstituted cyclopropane **13** while the known thermal synthesis provided either a 1:1 mixture of two diastereomers^[11a] or a mixture of **13** and an isomeric furan derivative.^[11b] It is noteworthy that the expected *cis*–*trans* isomerization was not observed.

Our method is not only suited for the preparation of monocyclic cyclopropanes. Thus, we also developed a straightforward route to highly strained bicyclic molecules. Starting

with commercially available hydroxymethylcycloalkanes **14a–c** we prepared the benzoyl[*n*.1.0]alkanes **15a–c** in few steps and with good to excellent yields (Scheme 4). Furthermore, the cyclization proceeds in a fully diastereoselective manner to the *exo* compounds, as proven by NOE NMR experiments and in the case **15b** also by a crystal structure analysis.



Scheme 4. Preparation of [*n*.1.0]bicycloalkanes **15**. 1) pyridinium chlorochromate; 2) PhC(OSiMe₃)(CN)Li; 3) Ms₂O/pyridine, 4) CH₂Cl₂, *hν* ($\lambda \geq 300$ nm), *N*-methylimidazole (2 equiv).

After exploring the synthetic scope of this very efficient method, whose most important results are described herein, for the diastereoselective preparation of highly substituted cyclopropanes, we hope to soon report on applications for the synthesis of more complex target molecules.

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Formation of Super Wires of Clusters by Self-Assembly of Transition Metal Cluster Anions with Metal Cations

Takayuki Nakajima, Atsushi Ishiguro, and Yasuo Wakatsuki*

The self-assembly approach to the construction of supramolecules or extended frameworks based on coordination complexes is one of the major current research areas in inorganic and organometallic chemistry.^[1] In the vast majority of such compounds, the molecular building blocks are held together by strong metal–(linking ligand)–metal bonding interactions or weaker forces such as hydrogen bonding between ligands coordinating to the different metal units. In some cases, however, the metal–metal stacking force of square-planar complexes can lead to stacklike, one-dimensional (1D) metal–metal bonds in the solid state. Thus, there has been a series of reports on (Pt–Pt)_∞ chains in which metal–metal separations indicative of weak interactions or of discrete bonds have been found.^[2] A similar 1D stacking polymer [{Ru(CO)₄}]_∞ has been structurally characterized by powder diffraction,^[3] and a 1D Rh–Rh polymeric complex has been prepared by the electrochemical reduction of an Rh^{II}–Rh^{II} dimer that only has acetonitrile ligands.^[4] This reaction has been explained as a radical polymerization of an unstable [Rh₂^{I,II}] species generated at the electrode. Crystals of a nonstacked zigzag chain of Co–Cu atoms have been prepared by a simpler route, that is, the reaction of Na[Co(CO)₄] with CuCl.^[5] Herein we report a new class of 1D complexes that consist of high-nuclearity cluster species and have infinite, heteroleptic metal–metal bonded chains. This unprecedented “super wire” has been prepared by alternative self ordering of anionic cluster complexes with a cationic metal species.

In 1983, Heaton and co-workers reported an interesting observation from NMR spectroscopy which was that on addition of Ag⁺ ions to a solution of [Rh₆C(CO)₁₅]^{2–}, the oligomeric species [Ag_n{Rh₆C(CO)₁₅}]^{n–} (*n* > 3) is formed, although the crystals that they isolated were from a structurally simpler sandwich-type complex [Ag{Rh₆C(CO)₁₅}]^{3–}.^[6] Therefore, it appeared interesting to us to examine a similar reaction of the analogous ruthenium clusters because the Ru₆ core is hexagonal whereas the Rh₆ core has a trigonal prismatic structure. It was known that the reactions of high-nuclearity ruthenium cluster anions with Ag⁺^[7] and Cu⁺ ions^[7a, 8] gave sandwich-type complexes such as the rhodium complex isolated by Heaton. However, almost all of these isolated ruthenium products are stabilized by the inclusion of a chloride ligand from the [PPN]Cl (PPN = N(PPh₃)₂⁺) used in the reactions.

We wondered what the product would be if chloride is excluded from the reaction system, thus, we attempted the reaction of the hexanuclear dianionic ruthenium cluster [PPN]₂[Ru₆C(CO)₁₆] ([PPN]₂**1**) in THF, with an equivalent

of AgNO₃ at room temperature. Over 12 h a characteristic $\tilde{\nu}(\text{CO})$ band at 1998 cm^{–1} in the IR spectrum gradually increased while that of **1** at 1973 cm^{–1} disappeared completely, during this time the solution remained homogeneous. On evaporation of the solvent the crude micro-crystals obtained in 97% yield had the composition [PPN][AgRu₆C(CO)₁₆] ([PPN]**2**). This complex is soluble in acetone and probably has an oligomeric structure in solution as observed by Heaton for the rhodium complex.^[4] The solid-state IR spectrum of [PPN]**2** is very similar to that in solution: it shows the $\tilde{\nu}(\text{CO})$ band, though broader than the corresponding peak in solution, at 1999 cm^{–1} (KBr). Dark red crystals grown from acetone/methanol have the X-ray structure shown in Figure 1.

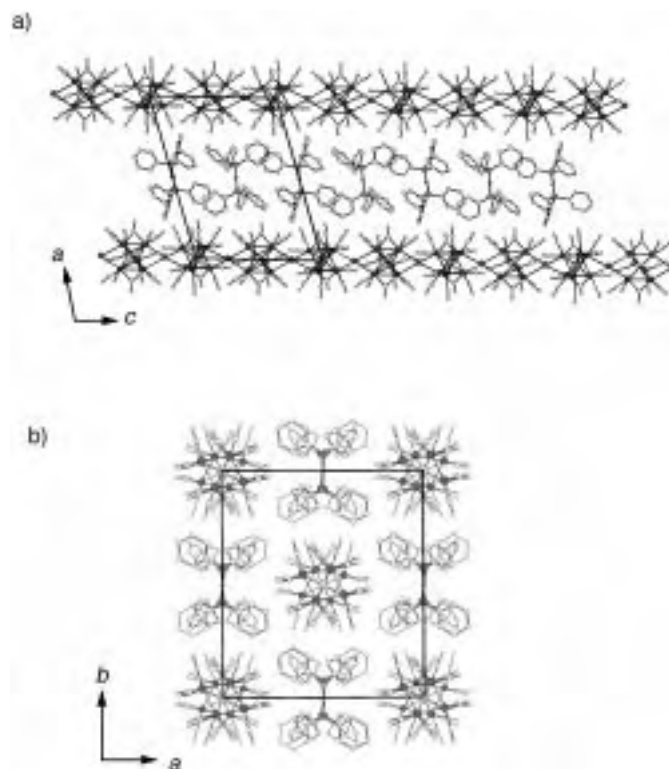


Figure 1. Crystal packing of [[PPN]**2**]_∞ viewed along a) the *b* axis and b) the *c* axis.

The infinite chains of alternating ruthenium clusters and silver ions are separated from each other by layers of PPN cations (Figure 1a). The view along the polymer-chain axis (Figure 1b) indicates that the Ru cluster and PPN are comparable in size which probably aids the crystal packing of [[PPN]**2**]_∞. Looking closer at this rigid metal chain (Figure 2), one notices that the bridging silver atom has a distorted tetrahedral orientation, the dihedral angle Ag–Ru12–Ru13/Ag–Ru12*–Ru13* being 49.9°. There is a point of inversion at the carbido center of the Ru₆ core, as well as at the silver atom, so that only three Ru atoms and one Ag atom are crystallographically independent. The Ag–Ru12 and Ag–Ru13 bond lengths are 2.9185(4) and 2.9425(4) Å, respectively. The edge bridged by the silver atom, Ru12–Ru13, is 3.046(1) Å, which is distinctly longer than the five independent Ru–Ru bonds (av. 2.907 Å). The polymeric complex with the PPh₄ cation [[PPh₄]**2**]_∞ was

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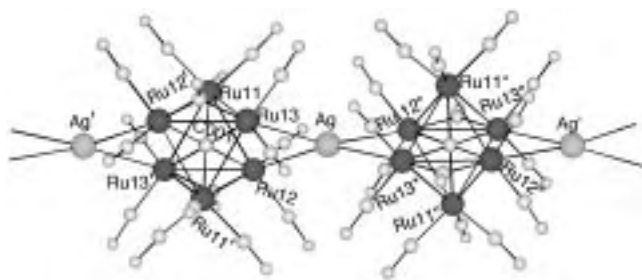


Figure 2. A section of the structure of anion **2** in $[\text{PPN}]_2$. Selected interatomic distances [Å] and angles [°]: Ag–Ru12 2.9185(4), Ag–Ru13 2.9425(4), Ru11–Ru12 2.8903(5), Ru11–Ru13 2.9348(6), Ru12–Ru13 3.046(1), Ru11'–Ru12 2.9405(6), Ru11'–Ru13 2.9006(5), Ru12–Ru13' 2.8545(4), C001–Ru11 2.0372(4), C001–Ru12 2.0856(4), C001–Ru13 2.0888(4); Ru12–Ag–Ru13 62.62(1).

synthesized in the same way from $[\text{PPh}_4]_2\mathbf{1}$ and AgNO_3 in 93 % yield and structurally characterized. The anion in the solid state has a structure quite similar to that of $[\text{PPN}]_2$.

No change was observed spectroscopically on heating an acetone solution of $[\text{PPN}]_2$ at 60 °C for 12 h and $[\text{PPN}]_2$ was recovered quantitatively. In contrast, more soluble $[\text{PPh}_4]_2$ did show some reactivity; when $[\text{PPh}_4]_2$ (50 mg) was suspended in MeOH (20 mL) at 60 °C, the solution soon became homogeneous and the IR spectra began to show a slow change. After 12 h a dark red crystalline complex was isolated from this solution in around 42 % yield. This was not the recovered polymeric or oligomeric complex but had the composition $[\text{PPh}_4]_2[\text{AgRu}_6\text{C}(\text{CO})_{15}]$ ($[\text{PPh}_4]_2\mathbf{3}$) resulting from the loss of one CO ligand per Ru_6 unit. The overall structure of anion **3** (Figure 3), as determined by

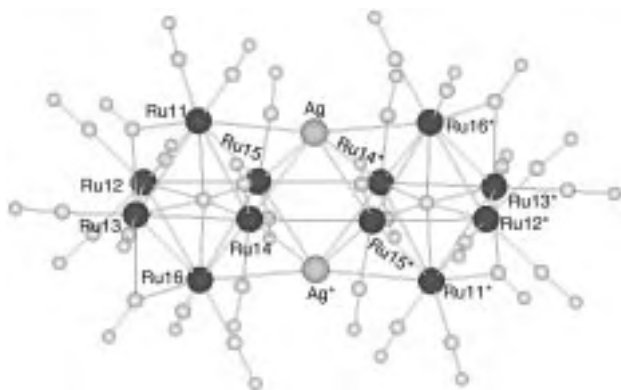


Figure 3. Structure of anion **3** in the crystal. Selected interatomic distances [Å] and angles [°]: Ag–Ru11 2.883(2), Ag–Ru14 2.848(1), Ag–Ru15 2.826(2), Ag*–Ru16 2.881(2), Ag*–Ru14 2.874(2), Ag*–Ru15 2.816(2), Ru14–Ru15* 3.033(2), Ru14–Ru15 3.222(2); Ru14–Ag–Ru15 69.20(4), Ru14*–Ag–Ru15 64.29(4), Ru14–Ag–Ru15* 64.77(4), Ru14*–Ag–Ru15* 68.97(4), Ag–Ru14–Ag* 77.06(4), Ag–Ru15–Ag* 78.36(4).

single-crystal X-ray analysis, turned out to be very similar to that of the mixed-metal palladium–ruthenium cluster $[\text{PPN}]_2[\text{Pd}_2\text{Ru}_{12}\text{C}_2(\text{CO})_{30}]$ recently prepared from $[\text{PPN}]_2\mathbf{1}$ and $[\text{Pd}(\text{CH}_3\text{CN})_4]^{2+}$.^[9] There is a crystallographic center of symmetry at the center of the molecule **3** (mid point between Ag–Ag*). Two Ag atoms bridge two Ru_6 moieties by capping the trigonal faces. Each Ag atom has, therefore, six Ag–Ru bonds ranging from 2.816(2) to 2.883(2) Å. As in the case of

the Pd analogue, the atoms Ru14 and Ru15 (and Ru14* and Ru15*) are interacting with the two bridging metals (Ag) and are thus no longer bonded to each other, the Ru...Ru distance being 3.222(2) Å.

In conclusion, we have shown that high nuclearity anionic clusters can undergo self-assembly with cationic metal species into a novel 1D polymeric form in the solid state. This cluster wire is remarkably stable: dissolution into oligomer and reformation of the infinite chain can be repeated at room temperature without any decomposition. Only after prolonged heating in solution does the polymeric complex with a PPh_4 cation rearrange to a dimeric form by loss of one CO ligand per cluster unit and concomitant shift of the Ag units from edge to face coordination of the Ru cluster core.

Experimental Section

All reactions were carried out in dry solvents under argon. All data collections for X-ray analysis were made on a Rigaku RAXIS-IV imaging plate diffractometer with graphite monochromated $\text{MoK}\alpha$ ($\lambda = 0.71073$ Å) radiation. Structures were solved by direct methods, expanded using Fourier techniques, and refined by full-matrix against $|F^2|$. All calculations were performed using the teXsan crystallographic software package (Molecular Structure Corporation (1992)). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-152134 ($[\text{PPN}]_2$), CCDC-152136 ($[\text{PPh}_4]_2$), CCDC-152135 ($[\text{PPh}_4]_2\mathbf{3}$). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

$[\text{PPN}][\text{AgRu}_6\text{C}(\text{CO})_{16}]$: A mixture of $[\text{PPN}]_2[\text{Ru}_6\text{C}(\text{CO})_{16}]$ (200 mg, 0.09 mmol) and AgNO_3 (16 mg, 0.09 mmol) in THF (30 mL) was stirred at room temperature for 12 h in a 100 mL Schlenk flask wrapped with aluminum foil. The reaction mixture was filtered through Celite before drying under vacuum, the residual red solid was washed with methanol to remove $[\text{PPN}]\text{NO}_3$ and yield red micro-crystals of $[\text{PPN}]_2$ (155 mg, 97%). Analytically pure material was obtained as dark-red plates by recrystallization from acetone/methanol at room temperature. IR(THF) $\tilde{\nu}(\text{CO})$ 1998(s) cm^{-1} ; elemental analysis (%) calcd for $\text{C}_{53}\text{H}_{30}\text{AgNO}_{16}\text{P}_2\text{Ru}_6$ (1713.05): C 37.16, H 1.77, N 0.82; found: C 37.15, H 1.74, N 0.79. Crystal data for $[\text{PPN}]_2$: $M_w(\text{unit}) = 1713.06$, monoclinic, space group $C2/c$ (no. 15), $a = 20.490(4)$, $b = 17.702(7)$, $c = 15.722(2)$ Å, $\beta = 104.09(1)^\circ$, $V = 5530(2)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 2.060$ g cm⁻³, $\mu = 20.4$ cm⁻¹, data collection at 20 °C, $R1 = 0.031$, $R2 = 0.038$ for 4730 data with $I > 4\sigma(I)$.

$[\text{PPh}_4]_2$: Dark red plates; IR(THF) $\tilde{\nu}(\text{CO})$ 1998(s) cm^{-1} ; elemental analysis (%) calcd for $\text{C}_{41}\text{H}_{20}\text{AgO}_{16}\text{P}_2\text{Ru}_6$ (1513.86): C 32.52, H 1.33; found: C 32.20, H 1.30. Crystal data for $[\text{PPh}_4]_2$: unit $M_w(\text{unit}) = 1514.46$, triclinic, space group $P\bar{1}$ (no. 2), $a = 15.938(6)$, $b = 22.029(9)$, $c = 15.775(9)$ Å, $\alpha = 99.23(3)^\circ$, $\beta = 107.65(2)^\circ$, $\gamma = 104.95(5)^\circ$, $V = 4925(5)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 2.055$ g cm⁻³, $\mu = 22.8$ cm⁻¹, data collection at 20 °C, $R1 = 0.052$, $R2 = 0.086$ for 9518 data with $I > 4\sigma(I)$.

$[\text{PPh}_4]_2[\text{Ru}_{12}\text{C}_2(\text{CO})_{30}\text{Ag}_2]$: A suspension of $[\text{PPh}_4]_2$ (50 mg, 0.033 mmol) in methanol (20 mL) was stirred at 60 °C for 12 h in a 100 mL Schlenk flask. The solvent was evaporated under reduced pressure and the residual dark red solid was purified by chromatography on SiO_2 (deactivated with 10 wt % H_2O). The dark red solution eluted with CH_2Cl_2 was collected and evaporated to dryness to yield dark red solid $[\text{PPh}_4]_2\mathbf{3}$ (21 mg, 0.007 mmol). Analytically pure material was obtained as dark red needles by recrystallization from CH_2Cl_2 /methanol. IR(THF) $\tilde{\nu}(\text{CO})$ 2033(s), 2017(s), 2002(s) cm^{-1} , elemental analysis (%) calcd for $\text{C}_{80}\text{H}_{40}\text{Ag}_2\text{O}_{30}\text{P}_2\text{Ru}_{12}$ (2971.70): C 32.32, H 1.36; found: C 32.12, H 1.38. Crystal data for $[\text{PPh}_4]_2\mathbf{3}$: $M_w = 2972.90$, triclinic, space group $P\bar{1}$ (no. 2), $a = 13.417(2)$, $b = 13.967(2)$, $c = 14.728(2)$ Å, $\alpha = 63.25(1)^\circ$, $\beta = 65.26(1)^\circ$, $\gamma = 87.17(1)^\circ$, $V = 2205.3(6)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 2.237$ g cm⁻³, $\mu = 25.4$ cm⁻¹, data collection at 20 °C, $R1 = 0.055$, $R2 = 0.058$ for 4537 data with $I > 2\sigma(I)$.

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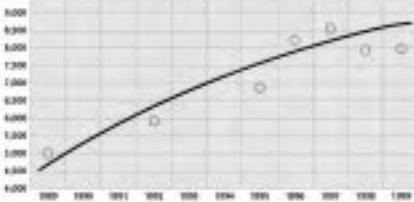


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Heteroepitaxial Growth of a Zeolite**

Tatsuya Okubo,* Toru Wakihara, Jacques Plévert, Sankar Nair, Michael Tsapatsis, Yoshifumi Ogawa, Hiroshi Komiyama, Masahiro Yoshimura, and Mark E. Davis

Zeolites contain molecular-sized void spaces within their crystal structures.^[1] Over 120 framework topologies have been recognized for zeolites and related materials.^[2] Because of their unique structures, zeolites and related microporous materials have been investigated as hosts for molecules, ions, and clusters, and interesting phenomena have been reported, especially for optical applications.^[3] The ability to provide for the heterogeneous connection of zeolite structures may enable the construction of multidimensional, nanospatial networks. Such nanospatial networks may serve as hosts to integrate molecular electronics and other molecular devices within the structures. Here we take the first step toward this goal by connecting one-dimensional cancrinite channels with zero-dimensional sodalite cages.

Certain zeolites are composed of the same building units but with different layer-stacking sequences.^[1] Thus far, such “intergrowth” phenomena have been investigated with micrometer-sized crystals such as ERI/OFF,^[4] MFI/MEL,^[5] FAU/EMT,^[6] and others.^[7–9] Recently, designed overgrowth for EMT/FAU on a micrometer scale was reported.^[10] To move from observations on a micrometer scale to applications that require control over larger length scales, such as optical devices, we focused on the construction of the first heterogeneous connection between two zeolites on a millimeter scale.

Zeolites composed of six-membered rings proved to be useful for the construction of multidimensional, nanospatial networks. Sodalite and cancrinite have structural similarities, since their aluminosilicate layers of six-membered rings are identical to each other, and the structures only differ in the stacking sequences of these layers (Figure 1). The ABCABC

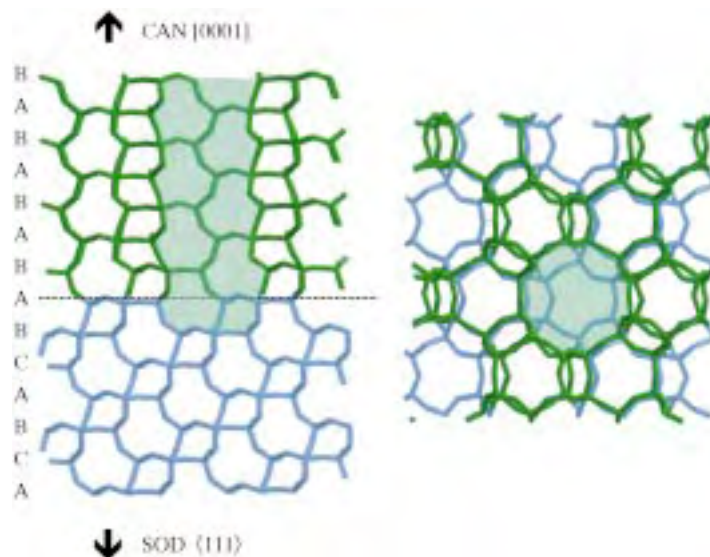


Figure 1. A model of heteroepitaxial growth of cancrinite on sodalite. The stacking sequence along the cancrinite [0001] direction is ABABAB (top), and that along the sodalite {111} direction is ABCABC (bottom). A composite view down the cancrinite [0001]/sodalite {111} direction is shown on the right. The shaded areas represent the connection of a sodalite cage and a 12-membered ring cancrinite channel on the left, and a single sodalite cage on the right.

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sequence generates sodalite cages, while the ABABAB sequence results in the one-dimensional 12-membered ring cancrinite channels that run along the direction perpendicular to the layer.^[1, 9] The ABCABC and ABABAB sequences are along the sodalite {111} axis and the cancrinite [0001] axis, respectively. The structural similarity enables us to connect these crystals in a heteroepitaxial manner. The concept of designed heteroepitaxial connectivity is not limited to the system demonstrated here; for example, other three-dimensional void spaces could be formed by controlling the stacking sequences from zeolites such as AABBC for chabazite, AABAAB for offretite, AABAAC for erionite, AABAABB for gmelinite, etc.

Millimeter-sized cubic sodalite crystals were synthesized at 973 K and about 80 MPa from a reaction mixture of composition 3SiO₂:3Al:2NaCl:9NaOH:97H₂O.^[11] The optical micrograph of a single crystal thus obtained is shown in Figure 2. The shape of the single crystals is a rhombic dodecahedron. A crystal with dodecahedral habit is expected to have {110} faces. The rhombus faces were verified to have {110} orientations by back reflection Laue X-ray photography.^[11a] Cancrinite was synthesized as described in the Experimental Section. When no sodalite crystals are added, aggregates of cancrinite crystals in the shape of hexagonal prisms are precipitated. The conditions necessary for heteroepitaxial growth of cancrinite on a sodalite substrate were

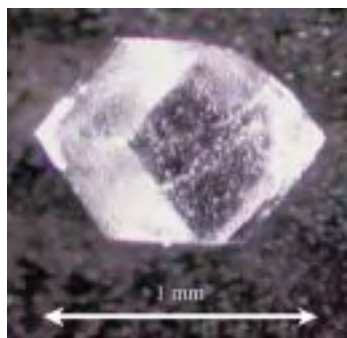


Figure 2. Optical photograph of a millimeter-sized sodalite single crystal grown under high-temperature, high-pressure hydrothermal conditions. The shape of the sodalite crystal is a dodecahedron, and the rhombus faces are sodalite {110} planes.

optimized by reducing the contribution of spontaneous nucleation. Such conditions were found by varying the time at which the sodalite crystals were introduced into the cancrinite synthesis solution. Millimeter-sized sodalite single crystals, prepared separately as described above, were placed in the cancrinite synthesis solution in the middle of the heating period. After a certain time, sodalite crystals overgrown with cancrinite were recovered and washed with distilled water. The changes in the morphology on sodalite faces were observed with a powder X-ray diffractometer (PXRD, Mac Science, MO3XHF²²), a field-emission scanning electron microscope (FE-SEM, Hitachi S-900), and transmission electron microscopes (TEM, JEOL JEM 2010F and JEM 4000FX-II) as a function of the cancrinite synthesis time. For the TEM observations, the sample was processed with a focused ion beam system (FIB, Micron, JFIB-2100). A cross-sectional specimen was prepared and thinned down by a gallium ion beam to only 200 nm, since the zeolite framework proved to be fragile at lower thickness. In addition to as-grown {110} faces, sodalite {111} surfaces were prepared by mechanical polishing.

By trial and error, conditions for shaping the surface topology were found for the sodalite faces. Typical synthesis conditions are summarized in Table 1. The best results were obtained when cancrinite was grown on a sodalite substrate

Table 1. Typical conditions for cancrinite heteroepitaxial growth on sodalite substrates (see Experimental Section).

Entry	Aging (at 298 K)	Preheating (at 358 K)	Growth (at 358 K)
1	2 h	18 h	48 h
2	2 h	16 h	48 h

for 48 h after preheating the cancrinite synthesis solution for 18 h at 358 K (entry 1). The single crystals were placed in the cancrinite synthesis vessel after the spontaneous nucleation and the greater part of crystal growth had been completed. An FE-SEM photograph of the synthesis product on a millimeter-sized sodalite {110} substrate is shown in Figure 3. This figure shows the formation of nanocrystals of cancrinite, identified by PXRD, with regular hexagonal-prism shape. The crystals are homogeneous in size, and the length-to-diameter ratio is relatively constant. Apparently, the supersaturation in the

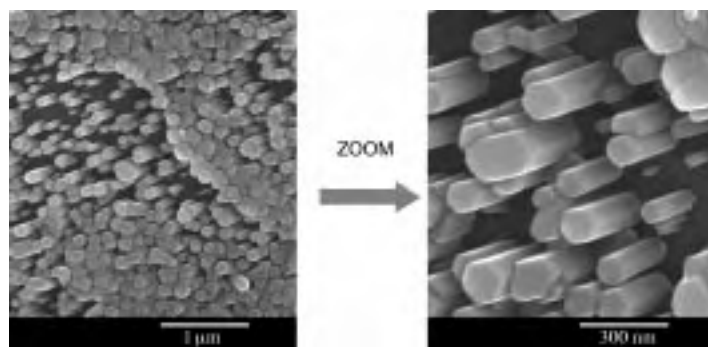


Figure 3. FE-SEM photographs of synthesis products on a sodalite {110} substrate. The cancrinite crystals in the shape of hexagonal prisms grow in parallel and have the same orientation in the basal plane.

synthesis medium was low enough to allow the formation of well-faceted crystals. The growth rate in the pore direction was higher than that in the basal plane of cancrinite, and this resulted in crystals with a nearly prismatic shape. The crystals grow in parallel and have the same orientation in the basal plane. In particular, the main axis of the crystals growing on sodalite {111} faces should be perpendicular to the substrate, while the crystals growing on the {110} faces should be inclined with a constant tilt angle of around 35°. This angle corresponds to that between the [011] and [111] directions in cubic crystal. These results strongly support epitaxial growth of cancrinite crystals on sodalite crystal surfaces.

The orientation of cancrinite crystals, synthesized under the conditions of entry 1 in Table 1, was determined by examining cross sections of the sodalite substrate by TEM. As soon as the focus and the astigmatism were adjusted, TEM photographs and SAED patterns were recorded under low-dose conditions to avoid destroying the crystal structure. The results revealed that the cancrinite grew heteroepitaxially on the sodalite substrate. A TEM photograph of the cross section of the sodalite {111} plane is shown in Figure 4a. Dense and well-aligned cancrinite crystals grow perpendicularly to the substrate surface with height of around 200 nm. SAED patterns in the sodalite region, apart from the overgrown layer, are taken along the [125] zone axis. All the spots can be indexed with the cubic unit cell of sodalite. On shifting the beam spot toward the cancrinite region, while keeping all conditions unchanged, weak spots were detected among the strong spots of the cubic structure (Figure 4b). The new spots can be indexed to the [2112] zone axis. A composite electron-diffraction simulation along the sodalite [125]/cancrinite [2112] zone axis is shown in Figure 4c. All the spots in Figure 4b correspond well with the simulated results in Figure 4c. The superposition of spots of both structures reveals the coincidence of planes $(1\bar{2}1)_{\text{SOD}}// (01\bar{1}0)_{\text{CAN}}$ and $(210)_{\text{SOD}}// (2\bar{1}\bar{1}1)_{\text{CAN}}$. The following orientation relationships between the two systems are obtained: cubic(111)/hexagonal(0001), cubic($1\bar{2}1$)/hexagonal($01\bar{1}0$), cubic($2\bar{1}\bar{1}$)/hexagonal($10\bar{1}0$). The unit-cell orientation relationships correspond to the epitaxial overgrowth of cancrinite crystals on the sodalite substrate, as shown in Figure 1.

Here we showed that the heteroepitaxial growth of cancrinite on millimeter-sized sodalite single crystals has

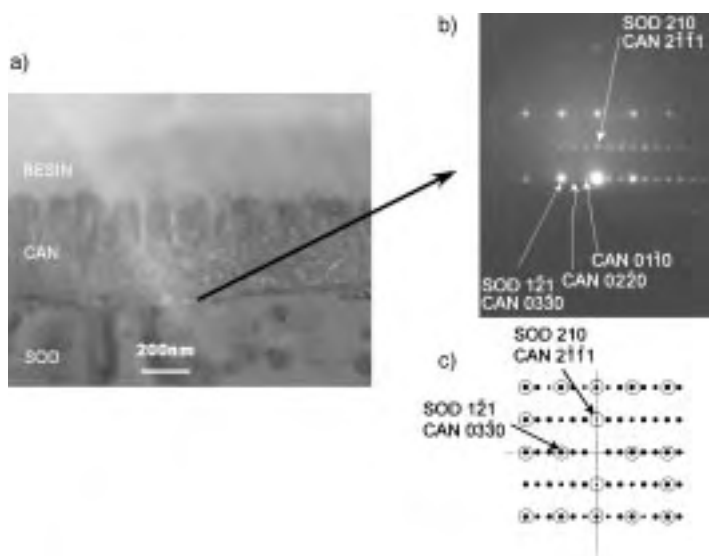


Figure 4. A TEM photograph and an SAED pattern of a cross section of a layer overgrown on a sodalite [111] substrate. a) The substrate is sodalite [111] prepared by mechanical polishing. The cancrinite crystals grow perpendicular to the sodalite [111] substrate. b) An SAED pattern recorded along the sodalite [125] zone axis. Spots due to cancrinite and sodalite are observed and indexed. c) A composite electron-diffraction simulation along the sodalite [125]/cancrinite [2112] zone axis. The spots resulting from superposition of diffracted beams from sodalite and cancrinite crystal planes are circled.

been accomplished. To the best of our knowledge, these results are the first to show the feasibility of preparing in-plane and out-of-plane oriented zeolite films with channels perpendicular to the substrate. These composite structures suggest a pathway toward the fabrication of multidimensional, nanospacial networks.

Experimental Section

The synthesis consists of aging, preheating without sodalite substrates, and growth with sodalite substrates. The starting solution had the composition $34\text{SiO}_2:2\text{Al}:50\text{NaNO}_3:200\text{NaOH}:2000\text{H}_2\text{O}$. First, aluminum powder, $0.1\text{ }\mu\text{m}$ in size, was added to a concentrated solution of NaOH in a Teflon vessel and dissolved completely. In another Teflon vessel, SiO_2 (Cab-O-Sil M-5), NaNO_3 , and the remaining NaOH and distilled water were mixed until the solution became transparent. Then the former solution was added to the latter, and the mixed clear solution was stirred for 2 h. All these procedures were carried out at 298 K. After this aging step, the solution was heated at 358 K for 18 h without sodalite substrates. Then, sodalite was introduced, and the mixture heated at 358 K for 48 h. The product was washed with distilled water and dried at 358 K. When the preheating phase was shortened by 2 h (Entry 2 in Table 1), heterogeneous nucleation on sodalite was enhanced, and a densely accumulated cancrinite layer was formed.

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Rotaxane-Encapsulation Enhances the Stability of an Azo Dye, in Solution and when Bonded to Cellulose**

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Tim D. W. Claridge, and Harry L. Anderson*

The groups of Cram and Warmuth have shown that exotic high-energy intermediates such as cyclobutadiene, *ortho*-benzyne, and cycloheptatetraene can be stabilized by encapsulation inside calixarene-based cages.^[1] These results inspired us to attempt to encapsulate and stabilize more mundane species such as dyes^[2] and conjugated polymers^[3] by synthesizing rotaxanes^[4] in which the reactive π system of the dye or polymer is protected inside the cavity of a macrocycle. We have previously reported the synthesis of azo dye rotaxanes;^[2a-c, 5] however, two key questions remained unanswered: a) Does encapsulation improve the longevity of the azo chromophore? b) Does encapsulation detrimentally prevent the dye from binding to surfaces? Here we address these issues by reporting an efficient synthesis of a

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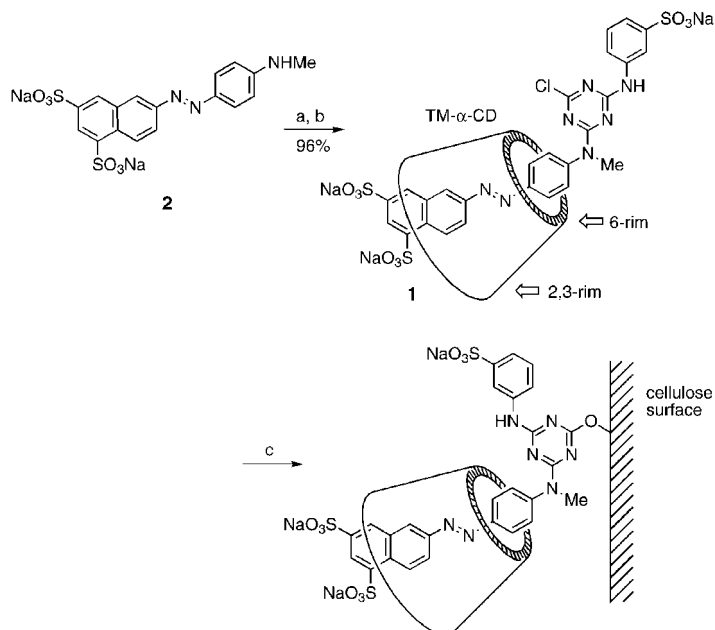
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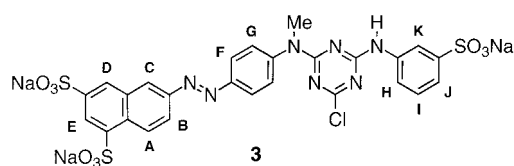
chlorotriazine-functionalized azo dye rotaxane. Encapsulation of this azo dye dramatically increases its stability towards bleaching, and does not prevent it from being covalently attached to cotton cloth (cellulose).

It is often desirable to covalently attach dyes to solid substrates, and this is commonly achieved by reacting an amine-substituted dye with 2,4,6-trichloro-1,3,5-triazine to give a chlorotriazine-functionalized "reactive dye" which couples with nucleophilic surface groups.^[6] This chlorotriazine chemistry works well in water, so it is compatible with the use of hydrophobic binding to direct rotaxane formation.^[7] The reactive dye rotaxane **1** was synthesized from amine **2** as shown in Scheme 1; the free reactive dye **3** was prepared by



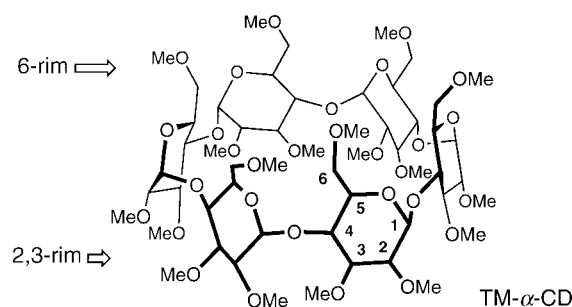
Scheme 1. Synthesis of rotaxane **1** and its covalent attachment to cellulose. a) TM- α -CD, $C_3N_3Cl_3$, H_2O , 0 °C, pH 6.5; b) 3-aminobenzenesulfonic acid, H_2O , 35 °C, pH 7.6; c) mercerized cotton, H_2O , 20 mM **1**, 0.7 M NaCl, 85 °C, pH 10, 24 h.

the same procedure in the absence of cyclodextrin. Compounds **1** and **3** are bright yellow, with λ_{max} in water at 364 and



350 nm, respectively. A simple dichlorotriazine end group would have been bulky enough to prevent the cyclodextrin from slipping off, but dichlorotriazines are hydrolytically unstable, so we displaced one of the chlorine atoms with 3-aminobenzenesulfonate to facilitate isolation and characterization. The remaining chlorine in **1** and **3** is stable to hydrolysis under neutral conditions, but reacts with cellulose at pH 10.

We used hexakis(2,3,6-tri-*O*-methyl)- α -cyclodextrin (TM- α -CD) in the synthesis of **1** to prevent coupling between the



chlorotriazine and hydroxy groups on the macrocycle. Methylation also extends the cavity,^[8] further shielding the encapsulated chromophore. TM- α -CD has the added benefit of binding extremely strongly to **2**,^[9] enabling the rotaxane to be prepared in quantitative yield without using a large excess of the cyclodextrin. Analytical thin-layer chromatography shows no sign of the free dye **3**, or any other colored by-products, in the crude reaction mixture, and rotaxane **1** was isolated in 96 % yield on a 1.5-g scale. A further advantage of the permethylated cyclodextrin is that excess TM- α -CD is readily removed from the reaction mixture by extraction into chloroform.

The conical shape of TM- α -CD results in the possibility of two stereoisomers for rotaxanes such as **1**, however in this case the rotaxane is formed as a single isomer^[10] (as shown by its sharp, well-resolved ^1H and ^{13}C NMR spectra, in both D_2O and $[D_6]DMSO$). COSY and NOESY spectra were used to assign the ^1H NMR spectrum in D_2O and to determine the three-dimensional geometry. The observation of NOEs from H_D , on the naphthalene unit, to H_3 and OMe_3 , on the CD, and from H_E to OMe_3 (Figure 1) proves that the wide 2,3-rim of the CD is over the naphthalene unit, whereas the NOEs from $H_{F/G}$ to OMe_6 , H_6 , H_6' , and H_5 show that the narrow 6-rim is over the *para*-phenylene unit, as depicted in Scheme 1. No NOEs are observed from OMe_2 to the aromatic protons because these six methoxy groups are directed away from the cavity, as noted by Harata et al.^[8] A space-filling representation of the energy-minimized structure of **1** (Figure 2) shows that the azo region of the chromophore is masked by the cyclodextrin.

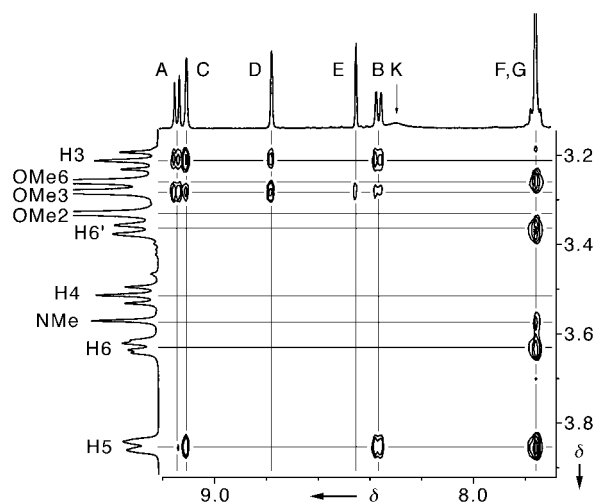


Figure 1. Part of the NOESY spectrum of **1** (500 MHz, D_2O , 298 K, 300 ms mixing time; all NOEs are negative).

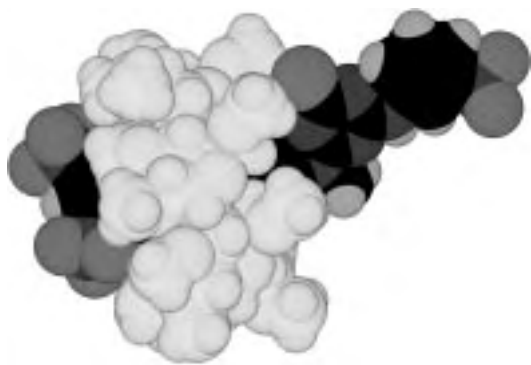


Figure 2. Energy-minimized structure (MM2 force field, CACHe 4.1.1) of rotaxane **1** (same orientation as in Scheme 1, with TM- α -CD pale gray).

The reactivity of rotaxane **1**, and the analogous free dye **3**, towards reductive bleaching was investigated by using aqueous sodium dithionite. This reagent bleaches azo dyes by reducing the azo link first to a hydrazine, then to two amine units.^[11] Test tube experiments immediately showed that solutions of the free dye **3** are rapidly bleached by dithionite, whereas the rotaxane **1** is unaffected. The rates of reaction were compared by monitoring the bleaching of solutions of **1** and **3** in UV cuvettes, giving the data plotted in Figure 3. The

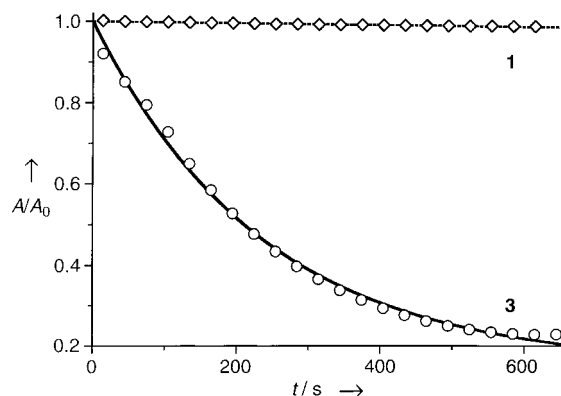


Figure 3. Reductive bleaching of **1** and **3** with aqueous sodium dithionite at 25 °C fitted to pseudo first-order decay curves with $k = 4.2 \times 10^{-3}$ and $2.3 \times 10^{-5} \text{ s}^{-1}$, respectively; A/A_0 is the normalized absorption at 500 nm; initial concentration of **1** and **3**: 0.1 mM; 0.5 M $\text{Na}_2\text{S}_2\text{O}_4$.

free dye is essentially destroyed after 15 min, whereas the rotaxane retains 90 % of its absorption even after 9 h. It is difficult to estimate the rate of bleaching for **1** because it is so slow, and the dithionite decomposes before it reacts with the rotaxane. From the initial rates, **1** appears to be more than 100 times less reactive than **3**. We also tested the reactivity of both dyes towards oxidative bleaching with hydrogen peroxide in the presence of catalytic iron(II) sulfate, a mixture known as Fenton's reagent^[12] (see decay curves in the Supporting Information). An orange intermediate is observed in both cases (probably an azoxide), followed by complete destruction of the chromophore. The free dye **3** gives an intense coloration after 10 min and is 90 % bleached after 50 min, whereas the rotaxane **1** shows only a slight rise in absorption, and is 90 % bleached after 6 h.

Samples of mercerized cotton were dyed yellow with aqueous solutions of compounds **1** and **3**, whereas no permanent coloration was produced by the nonreactive dye **2**, demonstrating that **1** and **3** bind covalently to cellulose. When cotton is dyed with **1** and **3** under identical conditions, the rotaxane gives a paler color than the free dye. The TM- α -CD evidently hinders coupling to the chlorotriazine, but this is a minor effect, and is easily compensated by using a more concentrated solution of the rotaxane, as illustrated by the photographs of cotton dyed with **1** (25 mM) and **3** (18 mM) in Figures 4a top and bottom, respectively. Images b–e in



Figure 4. Photographs of cotton samples dyed with rotaxane **1** (top) and free dye **3** (bottom), before (a) and after different times t of bleaching with $\text{Na}_2\text{S}_2\text{O}_4$ (1M): b) $t = 30$, c) $t = 90$, d) $t = 300$, e) $t = 1000$ s.

Figure 4 show the effect of bleaching both samples with sodium dithionite for increasing lengths of time: The sample dyed with **3** is almost completely bleached after 1 h, whereas that dyed with **1** is only slightly paler after 9 h. Treatment of similar cotton samples with Fenton's reagent resulted in a brown coloration of the cloth dyed with **3** after about 1 h, whereas that dyed with **1** was almost unaffected. Light-stability tests were carried out on a commercial fadeometer and showed that the cellulose-bound free dye underwent photo-bleaching about ten times faster than the cellulose-bound rotaxane.^[13]

The synthesis of a reactive azo dye rotaxane as a single isomer in quantitative yield on a gram scale and the demonstration that this rotaxane exhibits dramatically enhanced stability towards reductive bleaching, oxidative bleaching and photo-bleaching suggest that rotaxane-encapsulated dyes may have potential applications in areas where chromophore degradation needs to be prevented.

Experimental Section

1: Crushed ice (5 g) was added to a rapidly stirred solution of 2,4,6-trichloro-1,3,5-triazine (154 mg, 0.833 mmol) in acetone (5 mL). The resulting fine suspension was added dropwise to a solution of **2** (380 mg, 0.817 mmol) and TM- α -CD (1.16 g, 0.95 mmol) in water (50 mL) at 0 °C, while maintaining the pH at 6.5 (using HCl and NaHCO_3). After the pH of the solution ceased to fall the mixture was stirred for 20 min, adjusted to pH 7.6 and filtered while cold. A solution of sodium 3-aminobenzenesulfonate (163 mg, 0.833 mmol) in water (5 mL) was added to the reaction mixture, then the temperature was taken to 35 °C for 1 h, while the pH was maintained at 7.6. The mixture was washed with chloroform (5 $\times$ 50 mL), ultrafiltered in water (1.5 L) for 17 h using a membrane with a nominal molecular weight cut-off of 1000 (YM1, regenerated cellulose, from Millipore Ltd.), then evaporated to dryness to yield rotaxane **1** as an orange solid (1.58 g, 96 %). ^1H NMR (500 MHz, D_2O): $\delta = 9.12$ (d, $J = 9$ Hz, 1H), 9.08 (d, $J = 2$ Hz, 1H), 8.76 (d, $J = 1$ Hz, 1H), 8.44 (d, $J = 1$ Hz, 1H), 8.35 (dd, $J' = 9$, $J'' = 2$ Hz, 1H), 8.28 (brs, 1H), 7.73 (AA'BB' q, 4H),

7.57 (d, $J = 7$ Hz, 1H), 7.48 (d, $J = 7$ Hz, 1H), 7.40 (t, $J = 7$ Hz, 1H), 5.00 (d, $J = 3$ Hz, 6H), 3.83 (d, $J = 9$ Hz, 6H), 3.61 (dd, $J = 10$, $J' = 3$ Hz, 6H), 3.52 (s, 3H), 3.49 (t, $J = 10$ Hz, 6H), 3.34 (d, $J = 10$ Hz, 6H), 3.31 (s, 18H), 3.26 (s, 18H), 3.24 (s, 18H), 3.19 (t, $J = 10$ Hz, 6H), 3.01 (dd, $J = 10$, $J' = 3$ Hz, 6H); ^{13}C NMR (125 MHz, D_2O): $\delta = 169.1, 165.4, 164.0, 150.7, 150.5, 147.7, 143.8, 141.8, 141.5, 138.5, 133.9, 133.1, 131.7, 129.94, 129.93, 129.7, 128.9, 128.1, 124.9, 123.7, 121.3, 118.5, 117.4, 100.0, 82.4, 81.4, 81.1, 71.4, 71.1, 62.5, 59.0, 57.6, 39.1$; UV/Vis (H_2O): $\lambda_{\text{max}} = 364$ nm, $\lg \epsilon = 4.3$; ES-MS (negative): m/z : 964.2 [$\text{M}^{3-} + \text{Na}^+$].

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2-Pyridyldimethylsilyl as a Removable Hydrophilic Group in Aqueous Diels–Alder Reactions**

Kenichiro Itami, Toshiki Nokami, and Jun-ichi Yoshida*

During the last two decades water has been rediscovered as a most intriguing medium for organic synthesis.^[1] However, the execution of organic reactions in water is not straightforward since many organic compounds, reagents, and catalysts are insoluble or unstable in it. Therefore, many of the reported aqueous organic reactions have had to rely on the use of organic co-solvents at the expense of the many inherent advantages and unique properties of water, such as hydrophobic effects, hydrogen-bonding interactions, and high polarity.^[1]

During the course of our study on the development of multifunctional phase tags for solution-phase synthesis it was found that organic molecules bearing the 2-pyridyldimethylsilyl (2-PyMe₂Si) group are miscible with water when HCl is added.^[2,3] Molecular aggregation seems to be involved in their dissolution so as to minimize the energetically unfavorable contact between water molecules and nonpolar carbon chains. In addition, we have also established that the 2-PyMe₂Si group can be easily removed from organic molecules by oxidation with H₂O₂ to afford the corresponding alcohols.^[4]

We envisioned that if the 2-PyMe₂Si group works as a removable hydrophilic group and induces molecular aggregation in water, organic reactions in aqueous molecular aggregates should be possible when the reaction site is located on a hydrophobic side chain of the 2-PyMe₂Si-substituted molecule (Figure 1).^[5] The advantage of using the 2-PyMe₂Si

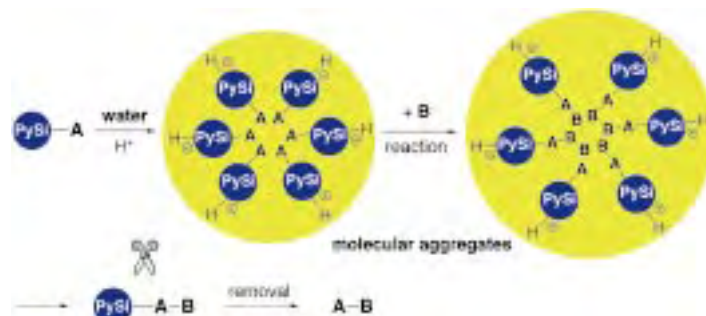


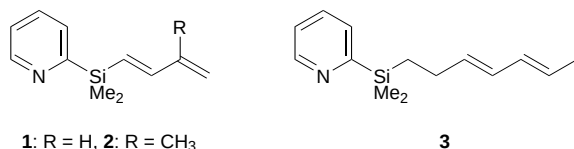
Figure 1. New strategy for aqueous organic reactions using a removable hydrophilic group.

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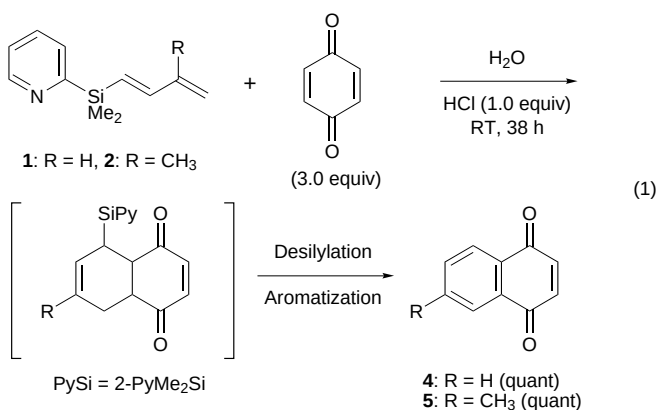
Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

group is apparent, as it can be readily removed from the molecules when required either by desilylation or oxidation. We chose an intermolecular Diels–Alder reaction of the 2-PyMe₂Si-substituted 1,3-dienes **1–3** to evaluate our strategy of using a removable hydrophilic group in aqueous organic reactions.^[1, 6–9]



First, the solution behavior of the 2-PyMe₂Si-substituted 1,3-dienes **1–3** in water was examined by dynamic light-scattering experiments on aqueous solutions (containing 1.0 equiv of HCl) of these dienes. These experiments revealed the presence of molecular aggregates of **1–3** with average hydrodynamic radii of 197, 138, and 307 nm, respectively. However, the determination of the exact structure of the molecular aggregates must await further investigations. The large radii observed can probably be attributed to nonordered structures of molecular aggregates in aqueous solution. The detection of molecular aggregates led us to explore aqueous reactions of **1–3**, irrespective of the structures of their molecular aggregates.

The Diels–Alder reactions of **1** and **2** with *p*-benzoquinone occurred at room temperature in water with simultaneous desilylation and aromatization to afford, respectively, naphthoquinones **4** and **5** quantitatively [Eq. (1)]. In these cases, an additional chemical operation to remove the 2-PyMe₂Si group was unnecessary.



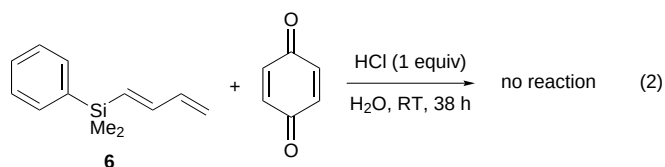
Several control experiments were conducted to assess the effect of the 2-PyMe₂Si group (Table 1). Decreasing the amount of HCl added slowed down the reaction enormously and only a trace amount of **4** was formed (entries 2 and 3). We contend that at least one equivalent of HCl is required for the 2-PyMe₂Si-substituted diene to form molecular aggregates and that the reaction probably occurs in the interior of aggregates where there are enhanced hydrophobic interactions,^[10] and not in the aqueous bulk phase.^[6] The use of H₂SO₄ also gave rise to a rate enhancement, but not as

Table 1. Aqueous Diels–Alder reactions of **1** with *p*-benzoquinone.^[a]

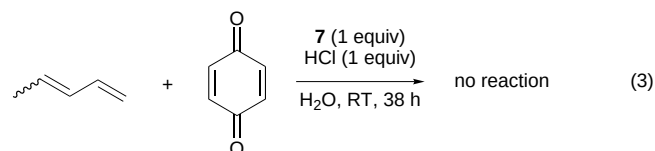
Entry	Solvent	Additive (equiv)	Time [h]	Yield of 4 [%] ^[b]
1	H ₂ O	HCl (1.0) ^[c]	38	quant
2	H ₂ O	HCl (0.2)	47	2
3	H ₂ O	–	89	4
4	H ₂ O	H ₂ SO ₄ (1.0)	38	73
5	Et ₂ O/toluene	HCl (1.0)	38	22
6	Et ₂ O/toluene	–	38	6

[a] All reactions were performed at room temperature using **1** (1.0 equiv, 1.0 M concentration) and *p*-benzoquinone (3.0 equiv). [b] Yields of isolated product. [c] The addition of 2.0 equivalents of HCl did not affect the rate and yield.

dramatic as with HCl (entry 4). The reaction carried out in organic solvent resulted in a much lower yield of the product (entries 5 and 6), which indicates the rate acceleration occurs in water. In contrast, the reaction with the PhMe₂Si-substituted diene **6** gave no Diels–Alder adduct at all in water [Eq. (2)].

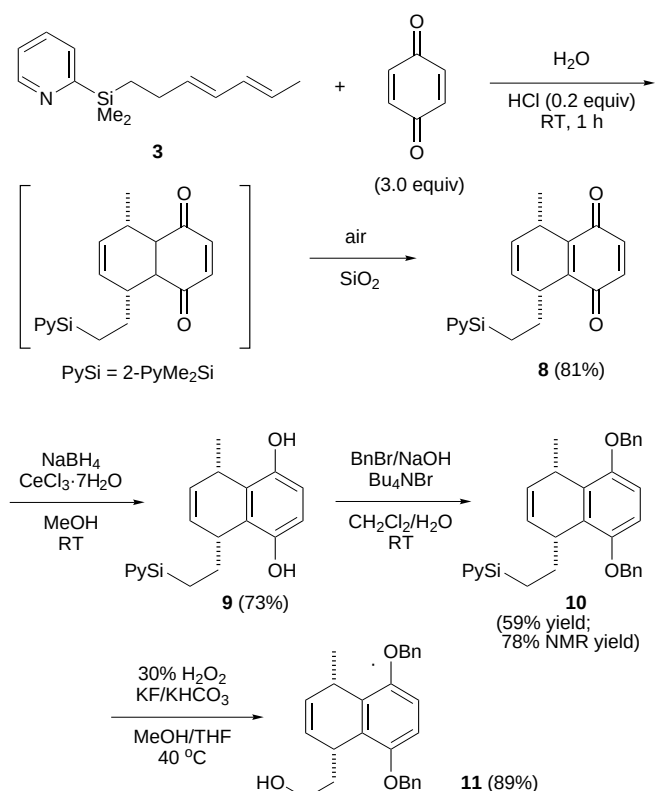


Next, we examined the aqueous reaction of 1,3-pentadiene with *p*-benzoquinone in the presence of protonated 2-pyridyldimethyloctylsilane (**7**) as a surfactant. The hard-to-dissolve 1,3-pentadiene dissolved in water when **7** and HCl were added. Thereafter, *p*-benzoquinone was added to the solution. However, in sharp contrast with the reaction of **1** or **2**, no cycloadduct was observed at room temperature [Eq. (3)]. It is apparent that the use of a reacting surfactant has an advantage in terms of reactivity over the combined use of an external surfactant.^[6b, 11]



The aqueous Diels–Alder reaction of **3** with *p*-benzoquinone was complete within one hour to give the cycloadduct **8** (Scheme 1).^[12] In this case a catalytic amount of HCl (0.2 equiv) was enough to promote the reaction. Interestingly, the formation of molecular aggregates (average hydrodynamic radii: 65 nm) was observed even at the end of the reaction. Moreover, the rate acceleration in water was again observed (12% yield of **8** in Et₂O/toluene).

The transformation of **8** was examined to test the chemical stability and removability of the 2-PyMe₂Si group (Scheme 1). The reduction of **8** afforded the substituted hydroquinone **9** in 73% yield. The protection of the phenolic hydroxyl groups with benzyl groups afforded **10** in 59% yield (78% by NMR spectroscopy). Importantly, the 2-PyMe₂Si group was unaf-



Scheme 1. Aqueous Diels–Alder reaction of **3** and removal of the 2-PyMe₂Si group. Bn = benzyl.

ected throughout these transformations, which indicates the reasonable chemical stability of this group. Finally, the oxidation of **10** with H₂O₂ afforded **11** in 89% yield without affecting the C–C double bond or eroding the stereochemistry at the allylic carbon atoms.

In summary, we have demonstrated the “proof-of-principle” of our strategy for aqueous organic reactions by utilizing the 2-PyMe₂Si group as a removable hydrophilic group. Importantly, the strategy described herein should not be limited to aqueous Diels–Alder reactions but could in principle be applied to other aqueous organic reactions as well.

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The Combination of Spontaneous Resolution and Asymmetric Catalysis: A Model for the Generation of Optical Activity from a Fully Racemic System**

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Dedicated to Professor Henri Kagan on the occasion of his 70th birthday

Considerable efforts have been devoted to the development of new chiral ligands owing to the growing importance of transition metal catalyzed asymmetric synthesis.^[1] Among these chiral ligands, diphosphanes have played a dominant role, in particular those possessing C₂ symmetry.^[2] We were interested in the possibilities offered by 1,1'-diphenyl-3,3',4,4'-tetramethyl-2,2'-biphosphole (**1**) (BIPHOS), first synthesized by Mathey et al. in 1986.^[3] This diphosphane combines the axial chirality generated by the biphenyl framework with the central chiralities of the phosphorus atoms. This implies the existence of six stereoisomers, corresponding to three pairs of enantiomers, which are in a fast equilibrium in

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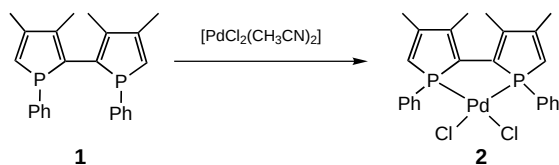
solution because of the configurational instability of the axial chirality and of the central chiralities of the phosphorus atoms.^[4] This stereolability is overcome in the solid state, and the stereoisomers have been fully characterized by an X-ray diffraction study.^[4] Herein we report the spontaneous resolution of the BIPHOS ligand by crystallization, the synthesis of the enantiomerically pure palladium complex [PdCl₂(biphos)], and its catalytic activity towards asymmetric allylic substitution.

The BIPHOS ligand **1** crystallizes as a conglomerate; each enantiomer crystallizes independently but no differences between these enantiomeric crystals are visible to the naked eye. X-ray diffraction studies of different single crystals^[4, 5] allowed the relative and absolute stereochemistry of the two enantiomers to be determined, corresponding to *S*[*RR*] or to *R*[*SS*].^[6] Single crystals of a rather large size (typically 50 to 150 mg) (Figure 1) were obtained and were used in the



Figure 1. Photograph of a single crystal (150 mg) of compound **1**.

synthesis of the optically pure complex [PdCl₂(biphos)]. Before every reaction, the purity of each crystal was checked by polarized light. To prevent the racemization that occurs at -60°C ,^[4] the reaction of a pure single crystal of **1** with one equivalent of [PdCl₂(CH₃CN)₂] (Scheme 1) was carried out at



Scheme 1. Synthesis of complex **2**.

-78°C in dichloromethane for 16 h. The ³¹P NMR spectrum of the reaction mixture, measured at room temperature, exhibited only one sharp singlet at $\delta = 33.4$, indicating the quantitative formation of complex **2**.^[7] This complex was isolated as a yellow solid in 93 % yield with $[\alpha]_{\text{D}}^{20} = +200$ ($c = 0.02$ in CH₂Cl₂). Furthermore, the optical rotation of the solution remained unchanged after 24 h at 40°C , giving an indication of the configurational stability of complex (+)-**2**. Thus, the stereochemistry of BIPHOS ligand **1** is stable once it is coordinated to the metal. The enantiomeric purity of complex **2** has not been evaluated; however, starting from

different single crystals of BIPHOS, the same absolute value of $[\alpha]_{\text{D}}$ was obtained for complex **2**. Furthermore, X-ray structure analysis of several single crystals of **2**, found in the same reaction mixture, show that they have the same absolute configuration. Therefore, we may consider that a single crystal of enantiomerically pure BIPHOS ligand in CH₂Cl₂ at -78°C reacts with [PdCl₂(CH₃CN)₂] to give the enantiomerically pure complex [PdCl₂(biphos)]. The molecular structure of complex (+)-**2**, which shows the *S*[*RR*]^[6] absolute configuration of the BIPHOS ligand, was determined by X-ray structure analysis^[8] (Figure 2). All structural parameters, distances, and angles are similar to those of the racemic complex.^[7]

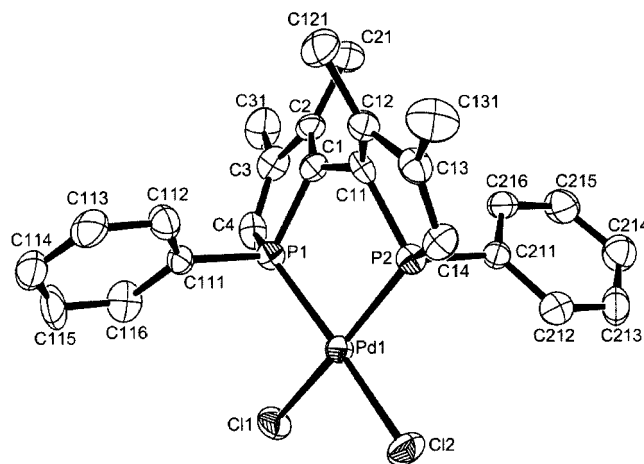
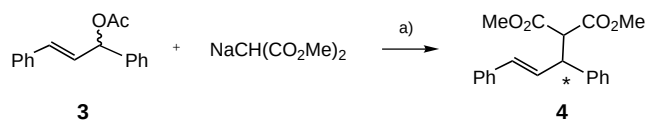


Figure 2. Molecular structure of *S*[*RR*]-(+)-**2** (ORTEP representation; the thermal ellipsoids correspond to 50 % probability).

The enantiomerically pure palladium complex **2** was used in the catalytic asymmetric allylic substitution^[9] of 1,3-diphenylprop-2-enyl acetate (**3**) with the anion of dimethyl malonate (Scheme 2). Our first study showed that a palladium complex



Scheme 2. Allylic substitution catalyzed by complex **2**. a) 1 % [PdCl₂(biphos)].

generated in situ from [[Pd(η^3 -C₃H₅)Cl]₂] and the racemic BIPHOS ligand proved to be a very efficient catalyst in dichloromethane at 35°C .^[4] When complex *R*[*SS*]-(-)-**2** was used under the same conditions, the allylic acetate **3** was smoothly converted after 24 h into the desired product (*R*)-**4** in 84 % yield and with 80 % *ee* (Table 1, entry 1). However, the yield could be increased to 93 % by using THF as solvent at 35°C , and even at a lower temperature (25°C ; Table 1, entry 2), without affecting the enantioselectivity. Furthermore, a similar experiment with the *S*[*RR*]-(+)-**2** complex gave the (*S*)-**4** product with the same yield (93 %) and *ee* (80 %, Table 1, entry 3). This again confirms the enantiomeric purity of complex **2**. The enantiomerically pure complex **2** prepared from a spontaneously resolved ligand proved to be

Table 1. Asymmetric allylic substitution of 1,3-diphenylprop-2-enyl acetate with the anion of dimethyl malonate, using 1 mol % of the palladium complex **2**.

Entry	Catalyst	Solvent	<i>T</i> [°C]	Conversion [% of 3] ^[a]	<i>ee</i> [% of 4] ^[b]
1	<i>R</i> [SS]-(-)- 2	CH ₂ Cl ₂	37	84	80 (<i>R</i>)
2	<i>R</i> [SS]-(-)- 2	THF	25	93	80 (<i>R</i>)
3	<i>S</i> [RR]-(+)- 2	THF	25	93	80 (<i>S</i>)

[a] Evaluated by ¹H NMR spectroscopy. [b] Determined by HPLC analysis using a chiral column (Pharmacir 7C).

as effective as CHIRAPHOS,^[10a] BPPF,^[10b] DPPBA,^[10c] and the BIPNOR^[10d]/Pd^{II} system in the catalytic asymmetric allylic substitution of 1,3-diphenylprop-2-enyl acetate with the anion of dimethyl malonate (Table 1). Our results provide an interesting example of the spontaneous generation of optical activity from a racemic mixture by crystallization of a molecule that is stereolabile in solution, followed by amplification in an enantioselective catalytic process. The crystallization of chiral ligands or chiral catalytic complexes as conglomerates has already been described,^[11] but to the best of our knowledge, the stereolabile BIPHOS ligand appears to be a special case. Because of the fast equilibrium between the two enantiomers in solution, the whole BIPHOS racemic mixture can be transformed into a single enantiomer,^[12] giving the enantiomerically pure catalytic complex quantitatively.

Experimental Section

1: The biphosphole was prepared as described in the literature.^[2b] To obtain single crystals, a very high purity of **1** is crucial. After purification by filtration through a short pad of silica gel (dichloromethane/pentane 70:30), the resulting oily residue was washed with pentane until a pale yellow solid was obtained. Subsequently, the slow evaporation of an undisturbed dichloromethane solution under argon gave single crystals of **1**.

2: A single crystal of BIPHOS **1** (0.050 mg, 0.13 mmol) was added to a stirred suspension of [PdCl₂(CH₃CN)₂] (0.033 mg, 0.13 mmol) in dichloromethane (5 mL) maintained at -78 °C. The mixture was stirred at -78 °C for 16 h, and then warmed to room temperature and filtered. The slow addition of pentane to the solution gave complex **2** as an orange microcrystalline solid (0.067 mg, 93 %), which was washed with pentane (2 × 2 mL). [α]_D²⁰ = +200 (*c* = 0.02 in CH₂Cl₂); ¹H NMR (CD₂Cl₂): δ = 1.87 (d, ⁴*J*_{PH} = 2.9 Hz, 6H; Me21, 121), 2.14 (d, ⁴*J*_{HH} = 1.5 Hz, 6H; Me31, 131), 6.63 (m, 2H; =CH-P), 7.40–7.87 (m, 10H; Ph); ³¹P NMR (CD₂Cl₂): δ = 33.4. Single crystals of *S*[RR]-(+)-**2** were obtained by the slow evaporation of a dichloromethane solution. Complex *R*[SS]-(-)-**2** was obtained in a similar way, starting from a single crystal of BIPHOS *R*[SS]-(-)-**1**.

General procedure for the allylic substitution: A solution of sodium dimethyl malonate resulting from the treatment of dimethyl malonate (0.148 mL, 1.29 mmol, 1.2 equiv) in THF (4 mL) with sodium hydride (80 % NaH, 1.07 mmol) was added to a solution of complex **2** (7 mg, 0.0123 mmol) and 1,3-diphenylprop-2-enylacetate (310 mg, 1.23 mmol) in THF (2 mL). After 24 h at room temperature, the resulting mixture was diluted with diethyl ether (5 mL) and quenched with a saturated aqueous NH₄Cl solution (5 mL). The aqueous phase was extracted with diethyl ether, the combined organic phases were dried over MgSO₄, filtered, and evaporated to give the crude product, which was purified by chromatography (SiO₂, ethyl acetate/pentane = 15:85). The enantiomeric excess was determined by chiral HPLC using a Pharmacir 7C column, hexane/isopropanol (90:10), 0.7 mL min⁻¹, *R*_f for the *S* isomer = 13.84 min, *R*_f for the *R* isomer = 15.15 min.

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Assembly of Nano-Scale Circular Supramolecular Arrays through $\pi-\pi$ Aggregation of Arc-Shaped Helicate Units**

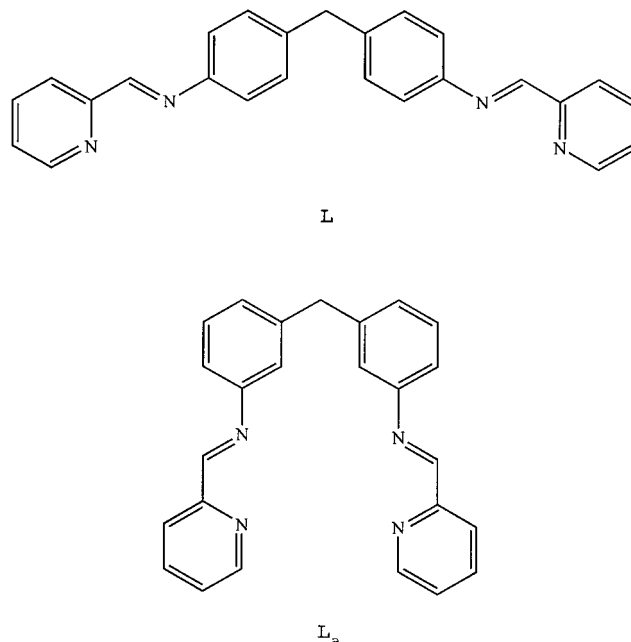
Laura J. Childs, Nathaniel W. Alcock, and Michael J. Hannon*

While not yet attaining the level of sophistication of biomolecular systems, the supramolecular synthetic approach is facilitating the construction of a wide-range of arrays of defined size and architecture whose scale is greater than that traditionally found in molecular chemistry.^[1] In this context metallo-supramolecular chemistry has enjoyed considerable success and a variety of nano-scale arrays have been constructed.^[2] The helical motif has provided an attractive forum for the development of design principles and discrete linear and circular helical systems have been designed.^[3] Covalent construction of the ligands places a limit on the size of the arrays and pentanuclear linear helicates^[4] (~2.5 nm length) and hexa- and octonuclear circular helicates^[5] (2–3 nm diameter) represent the largest monodisperse helicate systems reported. Alternative synthetic approaches and construction principles are required to circumvent these covalent synthetic limitations. One possible approach to generate nano-scale structures is to develop routes to further aggregate small supramolecular units into larger arrays using a second supramolecular event.^[6] To this end we have described the use of metal–ligand and $\pi-\pi$ interactions to achieve aggregation of metallo-supramolecular units into polymeric arrays.^[6] Williams and co-workers^[7] have also reported systems in which $\pi-\pi$ interactions link small helicate units into infinite linear chains in the solid state and Constable and co-workers^[8] have reported $\pi-\pi$ helicate dimerization. However, exerting sufficient control over this aggregation to afford monodisperse aggregates rather than polymeric assemblies remains a challenge. We have recently developed imine-based ligand systems through which a variety of supramolecular architectures may be assembled.^[9] The ease of synthesis of these ligand systems has allowed us to systematically probe the effects of modifications to the ligand backbone through which we are attempting to control the precise topography, or microarchitecture, of the arrays.^[9b,c] While investigating this we have chanced upon a means by which helicate topography may be used to control the way that helicate units aggregate into larger discrete (rather than polymeric) arrays, and herein we describe this method.

We have shown that the reaction of ligand L with tetrahedral metal ions leads to a solution equilibrium of two dimeric isomers; a helicate (*rac* isomer) and a metallo-

cyclophane (*meso* isomer).^[9c] We reasoned that the inherent twisting in the ligand could be enhanced by switching from a 4,4'-diphenylmethane spacer to a 3,3'-diphenylmethane and that consequently this modification should favor the formation of the helical isomer.

Ligand L_a was prepared in 89% yield by mixing two equivalents of 2-pyridinecarboxaldehyde and one equivalent



of 3,3'-methylenedianiline in toluene with ground 3 Å molecular sieves. Ligand L_a can also be prepared by mixing ethanolic solutions of the two starting materials. Reaction of L_a with [Cu(MeCN)₄]BF₄ in methanol yielded a red solution from which a red solid precipitated on cooling. Mass spectrometry (FAB and ESI) is consistent with the formation of a dimeric species of formula [Cu₂(L_a)₂](BF₄)₂ which could correspond to either the *rac* or *meso* isomer. Partial micro-analytical data is consistent with a formula {Cu(L_a)(BF₄)_n} and the red color (arising from an metal to ligand charge transfer (MLCT) transition) is characteristic of copper(II) in a bispyridylimine environment ($\lambda = 507$ nm, $\epsilon = 4000$ mol⁻¹ dm³ cm⁻¹). The ¹H NMR spectra of the compound have been recorded in both CD₂Cl₂ and CD₃CN solution. In both these solvents, at room temperature, a single set of resonance signals is observed. In CD₂Cl₂ at low temperature (253 K), a second set of resonances is observed. The assignment of helix and cyclophane is readily made from the splitting pattern of the central methylene unit.^[9c] The ratio of helix:cyclophane (*rac*:*meso*) is 9:1 indicating that the inherent ligand twisting has indeed favored the helical isomer. This ratio does not alter significantly when the temperature is lowered to 193 K.

Recrystallization of the compound from acetonitrile by diffusion of diethyl ether afforded crystals from which we confirmed the molecular structure by X-ray crystallography.^[10] The structure reveals a [Cu₂(L_a)₂]²⁺ helical cation (Figure 1).

Each copper(II) center occupies a four-coordinate pseudo-tetrahedral environment bound to two pyridylimine units, one

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Figure 1. View of the cation $[\text{Cu}_2(\text{L}_a)_2]^{2+}$, the copper coordination sphere is shown in black.

from each ligand. However, the 1,3 link in the spacer means that the ligands are unable to wrap precisely about the M–M axis and consequently a “bowed” (arc-shaped) helical conformation is adopted. Arc-shaped covalently prepared building blocks containing two hydrogen-bonding units have been described by Lehn and co-workers^[11a] and Whitesides et al.^[11b] and aggregate into cyclic supramolecular arrays. The arc-shaped topography has similar consequences for the solid-state aggregation of our helicates: in contrast to conventional linear helicates the arc-shaped helicates aggregate to form a cyclic array of four metallo-supramolecular units held together by π – π interactions^[12] (Figure 2). The diameter of the

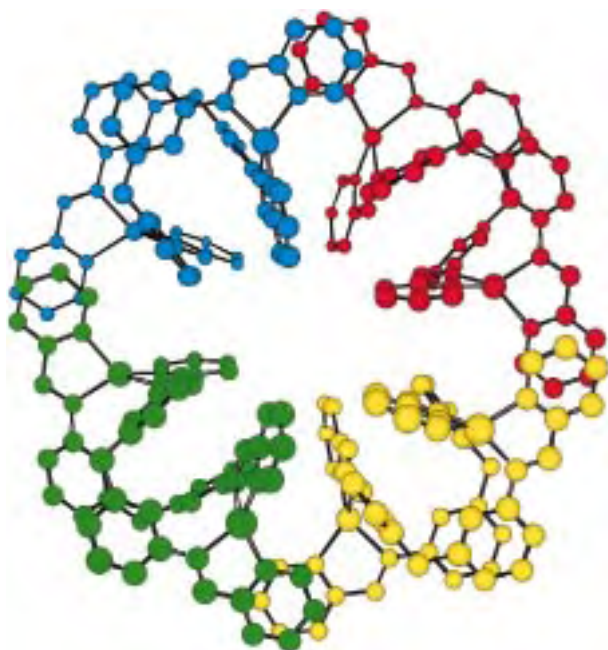


Figure 2. The cyclic array resulting from the aggregation of four $[\text{Cu}_2(\text{L}_a)_2]^{2+}$ helicates; each helicate is shown in a different color.

circular aggregate is ~ 2.5 nm (C–C; ~ 2.7 nm H–H) and four BF_4 counter anions are located in the internal cavity.^[13] The chirality of each helicate alternates around the circle so that the overall structure is achiral. The nano-scale structure nevertheless bears a striking resemblance to the circular

helical arrays recently reported,^[5] but it is achieved without the need for extensive covalent ligand synthesis.

While these circular aggregates form in the solid state, the weak nature of the non-covalent π – π interactions means that they lack the solution robustness of the circular helicates. Nevertheless, since weak, non-covalent interactions are capable of achieving order at surfaces and interfaces this does not necessarily provide a barrier to application or manipulation of the nanostructures. Extension of this topographical encoding approach to solution will require use of stronger non-covalent interactions (e.g. π -electron rich and deficient systems or multiple hydrogen bonds).

We have shown that by introducing curvature into the topography of the basic supramolecular unit, the aggregation into a larger discrete (rather than polymeric) array may be achieved. This result coupled with the ease of synthesis of the pyridylimine systems means that with judicious design quite large metallo-supramolecular nanostructures may be prepared rapidly from commercial materials.

Experimental Section

L_a : Ground 3 Å dried molecular sieves (5 g) and 3,3'-methylenedianiline (0.193 g, 0.975 mmol) were added to toluene (30 cm³) and stirred under a nitrogen atmosphere. 2-pyridinecarboxaldehyde (0.186 cm³, 1.947 mmol) was added and the mixture stirred at room temperature for 24 hours. The molecular sieves were removed by filtration and the filtrate concentrated by rotary evaporation to produce a yellow oil (0.326 g, 89%). ¹H NMR (CDCl_3): δ = 8.69 (d, J = 5.0 Hz, 1 H; H_6), 8.57 (s, 1 H; H_{imine}), 8.18 (d, J = 7.9 Hz, 1 H; H_3), 7.80 (td, J = 7.4, 1.5 Hz, 1 H; H_4), 7.35 (m, 2 H; H_5 , H_{Ph5}), 7.15 (m, 3 H; H_{Ph2} , H_{Ph6} , H_{Ph4}), 3.97 (s, 1 H; CH_2); MS (EI): m/z : 376 [M^+]; elemental analysis calcd. (%) for $\text{C}_{25}\text{H}_{20}\text{N}_4$: C 79.8, H 5.4, N 14.9; found: C 79.1, H 5.3, N 14.8.

$[\text{Cu}_2(\text{L}_a)_2](\text{BF}_4)_2$: Ligand L_a (0.107 g, 0.284 mmol) and $[\text{Cu}(\text{MeCN})_4](\text{BF}_4)$ (0.089 g, 0.284 mmol) were heated under reflux in methanol overnight. The solution was cooled to room temperature and treated with methanolic NH_4BF_4 (excess). On standing, a dark red solid precipitated and was collected by filtration and dried with diethyl ether (0.248 g, 83%). ¹H NMR (CD_2Cl_2 , 298 K): δ = 9.02 (s, 1 H; H_{imine}), 8.29 (d, J = 4.3 Hz, 1 H; H_6), 8.14 (d, J = 7.5 Hz, 1 H; H_3), 8.13 (d, J = 7.7, 1.5 Hz, 1 H; H_4), 7.52 (m, 2 H; H_5 , $\text{H}_{\text{Ph4/Ph6}}$), 7.11 (t, J = 7.6 Hz, 1 H; H_{Ph5}), 6.78 (d, J = 7.6 Hz, 1 H; $\text{H}_{\text{Ph4/Ph6}}$), 6.47 (s, 1 H; H_{Ph2}), 3.49 (s, 1 H; CH_2); MS (ESI): m/z : 967 $[\text{Cu}_2(\text{L}_a)_2(\text{BF}_4)]^+$, 440 $[\text{Cu}_2(\text{L}_a)_2]^{2+}$; MS (FAB): m/z : 967 $[\text{Cu}_2(\text{L}_a)_2(\text{BF}_4)]^+$ and 880 $[\text{Cu}_2(\text{L}_a)_2]^{2+}$; elemental analysis calcd (%) for $\text{Cu}_2\text{C}_{50}\text{H}_{40}\text{N}_8\text{B}_2\text{F}_8 \cdot 2.5\text{H}_2\text{O}$: C 54.7, H 4.1, N 10.2; found: C 54.7, H 3.7, N 10.0; UV/Vis: λ_{max} [nm] ($\epsilon/\text{mol}^{-1}\text{dm}^3\text{cm}^{-1}$) 507 (4000), 310 (31300), 240 (31000).

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A Dendritic Structure Containing a Designed Cleft which Controls Ligand Coordination Behavior in an Analogous Way to Proteins**

Michael J. Hannon,* Paul C. Mayers, and Paul C. Taylor*

Nature uses metal–ion coordination complexes to undertake many tasks. Frequently it imparts function by modifying the conventional behavior of a metal complex by incorporation within a protein superstructure.^[1] For example, by isolating heme groups in the center of globular proteins oxidative dimerization is prevented and *reversible* oxygen binding is achieved. Steric isolation owes much to the dimensions of such globular proteins which are much larger than the small molecules prepared by synthetic chemists. Dendrimers represent a class of monodisperse synthetic macromolecules^[2] which approach the dimensions of proteins and have been proposed as potential protein and enzyme mimics.^[3] For example, porphyrins have been encapsulated at the center of spherical organic dendrimers to create compounds analogous to globular electron-transfer proteins^[4] and then used as oxidation catalysts.^[5]

However, in nature, coordination sites are often not completely encapsulated in the core of a protein. For example, in carbonic anhydrase (CA) the N_3 zinc(II)-coordination site is situated at the foot of a cleft accessible to the solvent. The essentially hydrophobic protein cleft plays an important role in the catalytic cycle, by binding the substrate, creating a hydrogen-bonded solvent network to facilitate proton transfer, and expelling the hydrophilic product.^[6] Equally importantly this cleft modifies and controls the chemistry of the coordination site. Investigations of zinc(II) species with tripodal N_3 ligands (L) reveal a strong tendency to form $[\text{ZnL}_2]^{2+}$ complexes or hydroxy-bridged dimers.^[7, 8] In the enzyme the protein cavity sterically prevents the formation of these species and discrete mononuclear 1:1 complexes $[\text{ZnL}(\text{OH})]^+$ and $[\text{ZnL}(\text{OH}_2)]^{2+}$ result. We were interested to see if we could imitate this natural approach to modify and control the behavior of a transition metal complex. Rather than simply isolating a complex within a globular dendritic structure we have focused on the design of systems in which a dendritic unit could be used to generate a cavity around a metal complex.

We reasoned that blocking one direction of “growth” of a dendrimer would lead to a large cleft in the structure around the site of the “blockage”. If the metal binding site forms the blocking group, or is attached to it, then at high generation

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this site should be surrounded by a dendrimer cleft (see Figure 1). While conventional dendrimers are considered to be spherical at higher generations with small cavities in the bulk of the molecule,^[9] the dendrimers described herein are different: the cleft is quite distinct from the smaller conventional dendrimer cavities and should persist even when the dendrimer bulk becomes more densely packed.

To investigate this idea we have designed a series of dendritic ligands (Figure 1) containing a tripodal N₃ ligand (extending the CA analogy),^[10] and report herein the effect of the dendrimer on the complexation ability of the tripodal ligand.

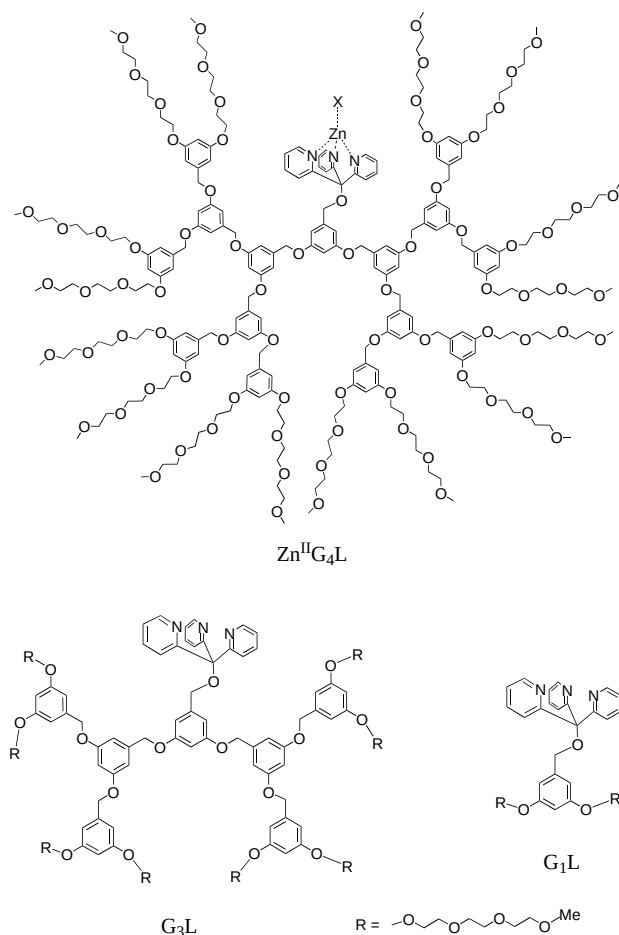
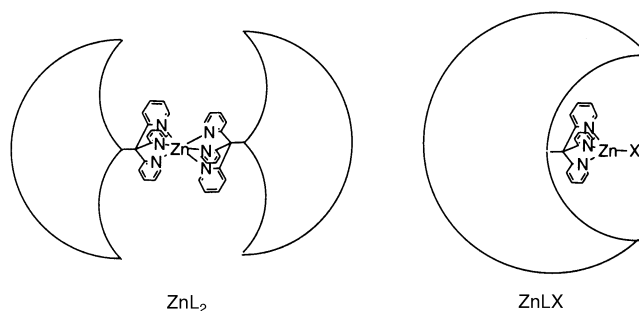


Figure 1. The N₃ binding site blocks the growth of the dendrimer as seen in the first and third generation ligands G₁L and G₃L; the resulting cleft is seen in the fourth generation complex Zn^{II}G₄L.

The dendrimers were prepared^[10] by a Fréchet-type^[11] convergent synthesis.^[12] The terminal polyether groups confer excellent solubility in a wide-range of solvents.^[10, 13] The zinc(II) complexes were prepared by treatment of a methanolic solution of the ligand with aqueous ZnCl₂. With a zinc(II) center the dendritic tripyridylmethanol unit (L) could form either an octahedral bis(L) complex [ZnL₂]²⁺ or a distorted tetrahedral mono(L) complex [ZnLX]ⁿ⁺ (where X is another ligand, e.g. Cl). If the dendritic structure does indeed form the desired cavity then at higher generation, as the dendrimer ligand (L) becomes larger, it should sterically prevent [ZnL₂]²⁺ formation and thereby favor the [ZnLX]ⁿ⁺ structure (as observed in the natural CA system).



Electrospray mass spectrometry has proved to be a powerful technique for analysis such dendrimer complexes and indicates that [ZnLX]ⁿ⁺ formation is indeed the case in solution (Figure 2).^[14] The mass spectra of the Zn^{II} complexes

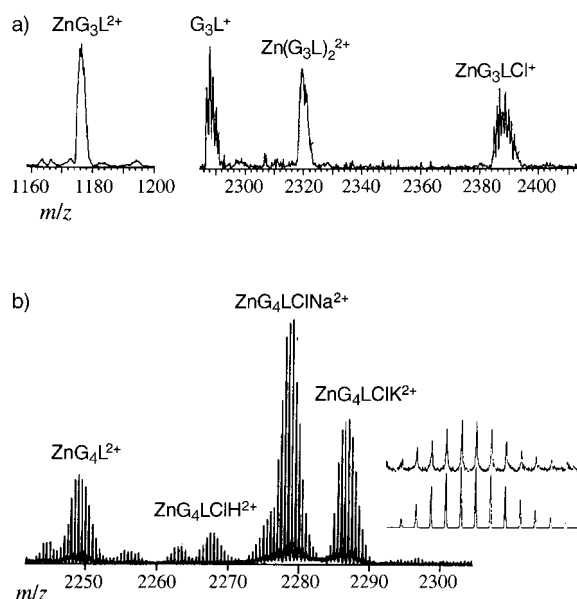


Figure 2. a) ES⁺ mass spectrum of the Zn^{II}G₃L complex; b) ES⁺ FT-ICR mass spectrum of Zn^{II}G₄L complex and (inset) an expansion of the [ZnLCIH]²⁺ signal together with the theoretical isotope pattern (below).

of the dendrimer ligands are dependent on the size of the dendrimer unit. Thus the mass spectrum of the Zn^{II}G₁L complex (not shown) is dominated by an intense signal corresponding to [ZnL₂]²⁺. At generation three, the mass spectrum of the Zn^{II}G₃L complex exhibits an intense signal at *m/z* 1176 corresponding to [ZnL]²⁺ but a more complex set of weak signals at *m/z* 2288, 2319, and 2387 corresponding to [LH]⁺, [ZnL₂]²⁺, and [ZnLCl]⁺, respectively, seem to indicate that the product is a mixture of 2:1 and 1:1 ligand/metal complexes (Figure 2a). Significantly different results are obtained for G₄L (Figure 2b). The positive electrospray ionization Fourier transform ion cyclotron resonance (ES⁺ FT-ICR) mass spectrum of the Zn^{II}G₄L complex exhibits signals at *m/z* 2249 [ZnL]²⁺, 2267 [ZnLCIH]²⁺, 2279 [ZnLCINa]²⁺, and 2287 [ZnLCIK]²⁺. No signals corresponding to [ZnL₂]²⁺ species were observed. The isotopic distribution of the signals matches the theoretical calculation in all four cases.

While this result does indicate that, as desired, the bulk of the dendrimer disfavors the formation of ZnL_2 species, the absence of the peak in the mass spectrum is not of itself definitive evidence. The required evidence comes from NMR spectroscopy titration studies.^[15] For the generation one ligand (G_1L) in dichloromethane solution (with 5% methanol),^[16] at a metal:ligand ratio of 1:2 only $[\text{ZnL}_2]^{2+}$ is detected. As the ratio of metal is increased to 1:1, resonance signals corresponding to $[\text{ZnLX}]^+$ start to appear but $[\text{ZnL}_2]^{2+}$ remains as a major species in solution.^[17] Even at a ratio of 10:1 resonance signals corresponding to the $[\text{ZnL}_2]^{2+}$ species remain. Almost identical behavior is observed for both the generation two and generation three ligands (G_2L and G_3L). This is illustrated for G_3L in Figure 3a. For the generation four ligand (G_4L ; Figure 3b) at a Zn:L ratio of 1:2, $[\text{ZnL}_2]^{2+}$ is still the dominant species, however, at a ratio of 1:1 only very trace amounts of $[\text{ZnL}_2]^{2+}$ are observed and the solution contains predominantly $[\text{ZnLX}]^+$. Equally dramatic effects are also observed in both CD_3OD and D_2O solutions, where for G_4L the $[\text{ZnL}_2]^{2+}$ complex is so disfavored that at a Zn:L ratio of 1:2, $[\text{ZnLX}]^+$ is the dominant species with free L and $[\text{ZnL}_2]^{2+}$ also present in the solution mixture. These NMR titrations in all three solvents reveal a quite dramatic change of behavior between generation three and generation four.

In conclusion evidence from NMR spectroscopy and ES-MS spectrometry confirm that dendritic units can be used to control and modify the conventional behavior of a complex in a similar way to that achieved by protein structures in nature. The generation four dendritic ligand ($\text{L} = \text{G}_4\text{L}$) is effective in

sterically isolating a coordinated metal ion and thus disfavors the formation of ZnL_2 species and leads to the formation of 1:1 complexes. The ligand also confers excellent solubility in a wide-range of solvents, including water. An attractive feature of this dendrimer-based approach is the potential both for systematically varying the nature and composition of the cleft and for extension to the isolation of different coordination environments as observed in a wide-range of enzymes.

Experimental Section

The dendritic ligands G_1L – G_4L were prepared as described in ref. [10] Electrospray mass spectra were performed on solutions of metal complexes prepared by adding excess dendrimer to the required metal salt (ZnCl_2). Proton NMR spectroscopy titrations were performed at constant ligand concentration, varying the metal salt concentration. $\text{Zn}(\text{ClO}_4)_2$ was used for the titrations in CD_2Cl_2 solution and ZnCl_2 in CD_3OD and D_2O .

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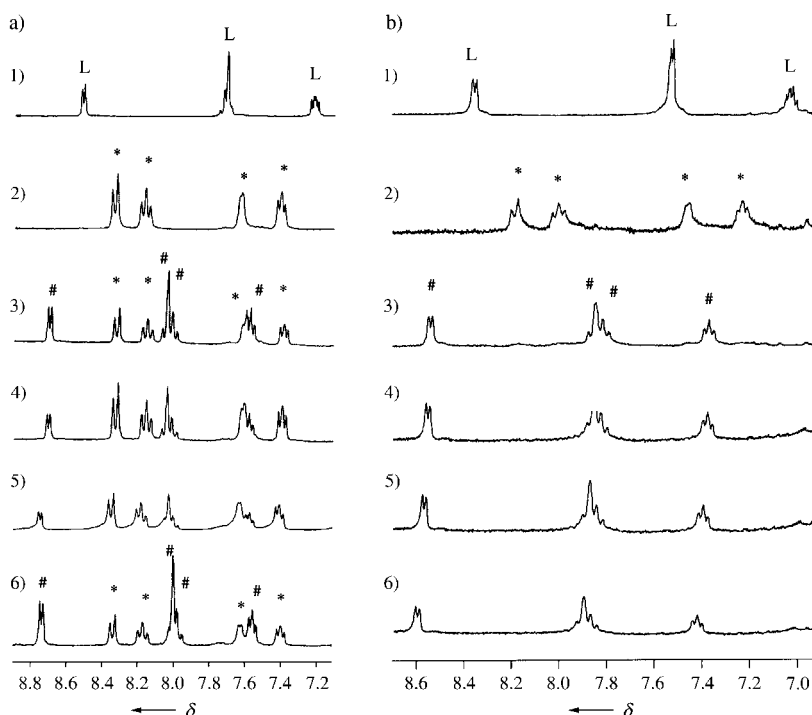


Figure 3. Pyridyl resonances in the ^1H NMR titration spectra of a) G_3L and b) G_4L with $\text{Zn}(\text{ClO}_4)_2$ in CD_3OD solution. 1) free ligand; 2) 0.5 equivalents of Zn^{II} ; 3) 1 equivalent of Zn^{II} ; 4) 2 equivalents of Zn^{II} ; 5) 5 equivalents Zn^{II} ; 6) 10 equivalents Zn^{II} . For clarity only the pyridyl resonances are shown; L = signals corresponding to the free ligand, * = signals corresponding to the 2:1 complex $[\text{ZnL}_2]^{2+}$, and # = signals corresponding to the 1:1 complex $[\text{ZnLX}]^+$.

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**[30]Metallacrown-10 Compounds:
 $[\text{Mn}(\text{C}_{14}\text{H}_9\text{N}_2\text{O}_3)(\text{CH}_3\text{OH})]_{10} \cdot 5 \text{CH}_2\text{Cl}_2 \cdot$
 $16 \text{CH}_3\text{OH} \cdot \text{H}_2\text{O}$ and
 $[\text{Fe}(\text{C}_{14}\text{H}_9\text{N}_2\text{O}_3)(\text{CH}_3\text{OH})]_{10} \cdot 3 \text{CH}_2\text{Cl}_2 \cdot$
 $12.5 \text{CH}_3\text{OH} \cdot 5 \text{H}_2\text{O}^{**}$**

Shi-Xiong Liu,* Shen Lin, Bi-Zhou Lin, Chi-Chang Lin, and Jian-Quan Huang

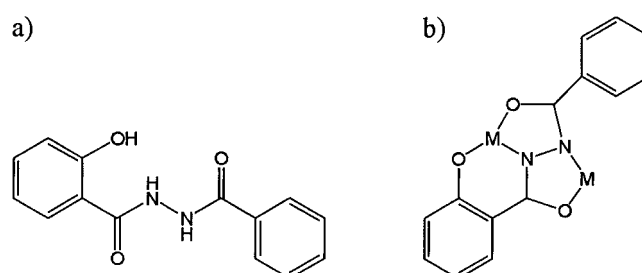
Metallacrowns are a new class of multinuclear clusters that are analogous to crown ethers in both structure and function.^[1, 2] One may substitute heteroatoms such as transition metals and nitrogen atoms for the methylene carbon atoms of the parent crown ether complexes to form metallacrowns.

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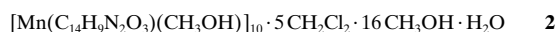
Therefore, there has been considerable interest in metallacrown chemistry owing to its potential applications in chemically modified electrodes, anion-selective separation agents, liquid-crystal precursors, and magnetic materials.^[3] Salicylhydroxamic acid (H_3shi) was used as the template ligand in the synthesis of the early metallacrowns. Many examples of this kind of metallacrown are known, for example, [9]metallacrowns-3,^[3, 4] [12]metallacrowns-4,^[1, 2, 5–8] and [15]metallacrowns-5,^[9] which have a $[\text{M}-\text{N}-\text{O}]_n$ repeat unit that forms a cyclic structure. Several compounds with the metallacrown structure type have been developed.^[10] Recently, an [18]metallacrown-6 using *N*-formylsalicylhydrazide (H_3fshz) as a ligand was reported.^[11] This metallacrown is the second kind of metallacrown with a $[\text{M}-\text{N}-\text{N}]_n$ repeating unit in which nitrogen atoms replace all the oxygen atoms in the cyclic structure.

Although some [9]metallacrowns-3, [12]metallacrowns-4, [15]metallacrowns-5, and an [18]metallacrown-6 are known, there has yet been no report of any [30]metallacrown-10. Taking the limitations of metallacrowns based solely on shi^{3-} and fshz^{3-} templates into account, we have greatly expanded the types of precursor ligands with the intention of modifying the ring size, as well as the electronic, magnetic, and other physical properties of the metallacrowns. We found that the choice of ligand plays an important role in preparing new metallacrowns with high nuclear number, such as the title [30]metallacrowns-10. Herein we provide a new potential pentadentate ligand *N*-phenylsalicylhydrazide (**1**) (H_3bzshz , Scheme 1 a) and the first two [30]metallacrowns-10, **2** and **3**.



Scheme 1. Ligand H_3bzshz (a) and basic binding sites in compounds **2** and **3** ($\text{M} = \text{Mn}, \text{Fe}$) (b).

The two title [30]metallacrowns-10 are also the second kind of metallacrown with a $[\text{M}-\text{N}-\text{N}]_n$ repeating unit, which may be more appropriately called an azametallacrown.^[12]



Single-crystal X-ray analysis of compound **2** (Figure 1) showed that there is a planar decanuclear 30-membered ring in the manganese metallacrown core. The 30-membered core ring exhibits crystallographic centrosymmetry and is a $[\text{Mn}-\text{N}-\text{N}]_{10}$ ring with neighboring $\text{Mn} \cdots \text{Mn}$ interatomic distances of 4.906(1)–4.986(2) Å. The size of the cavity in the 30-membered ring, measured between the opposite carbon atoms (less 1.57 Å for the van der Waals radii of carbon) is 6.80, 7.61, 6.39, 7.48, and 7.23 for C(13)–C(13a), C(26)–

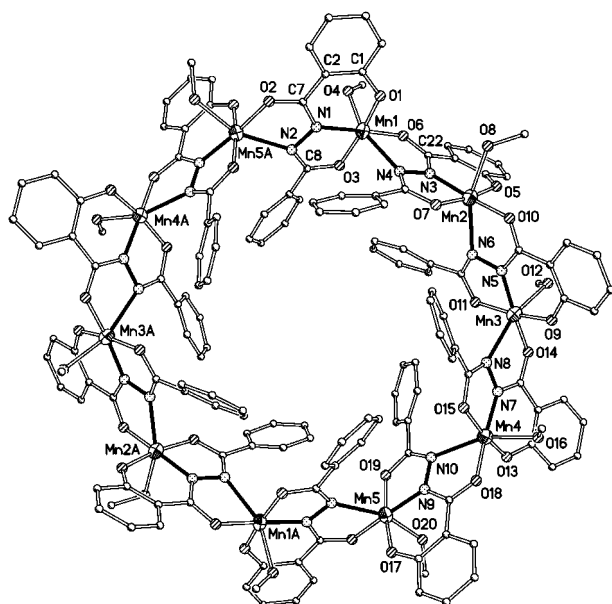


Figure 1. Perspective view of **2** (solvent molecules and all hydrogen atoms have been omitted for clarity). Selected bond lengths [Å] and angles [°]: Mn1–O1 1.878(5), Mn1–O3 1.888(5), Mn1–O6 1.969(5), Mn1–N1 1.959(6), Mn1–O4 2.267(6), Mn1–N4 2.350(6); O1–Mn1–O3 170.1(2), O3–Mn1–N1 79.7(2), O3–Mn1–O6 92.0(2), O1–Mn1–O4 90.7(2), N1–Mn1–O4 89.1(2), O1–Mn1–N4 88.7(2), N1–Mn1–N4 115.1(2), O4–Mn1–N4 155.9(2), O1–Mn1–N1 90.9(2), O1–Mn1–O6 97.7(2), N1–Mn1–O6 168.8(2), O3–Mn1–O4 92.2(2), O6–Mn1–O4 83.7(2), O3–Mn1–N4 92.5(2), O6–Mn1–N4 72.5(2); average neighbor Mn...Mn distance 4.953(2), average near-neighbor Mn...Mn distance 9.274(2); Mn...Mn...Mn 137.52–139.50.

C(26a), C(41)–C(41a), C(55)–C(55a), and C(71)–C(71a), respectively. The approximate dimensions of the oval-shaped cavity are approximately 6.39 Å in diameter at the entrance, approximately 13.19 Å (less 1.37 Å for the van der Waals radii of the manganese atom) at its largest diameter at the center of the cavity, and approximately 3.79 Å in depth.

All manganese atoms in compound **2** (Figure 1) are in a distorted octahedral MnN_2O_4 environment. The deprotonated ligand bzshz^{3-} acts as a multidentate ligand: one phenolate oxygen atom, one carbonyl oxygen atom, and one hydrazide nitrogen atom in the ligand are bound to each manganese atom, whereas the other carbonyl oxygen atom and the other hydrazide nitrogen atom in the ligand are chelated to an adjacent manganese atom. Therefore, the ligand induces the stereochemistry of the manganese(III) ions into a propeller configuration owing to the meridional coordination of the O1, N1, and O3 atoms of the ligand to the metal ion. The average axial manganese–oxygen/nitrogen distance of 2.310 Å in compound **2** is approximately 0.386 Å longer than the average base Mn–O/N distance of 1.924 Å. This typical Jahn–Teller elongation along the z axis of the manganese(III) ion was also observed in some manganese(III) compounds.^[10] All the manganese ions in the ring of the title compound **2** adopt a propeller configuration, despite the Jahn–Teller distortion of high-spin d^4 manganese(III) ions.

The crystal structure of compound **3** (Figure 2) is similar to that of compound **2** (Figure 1). The neighboring Fe...Fe interatomic distances in the 30-membered ring with an $[\text{Fe–N–N}]_{10}$ repeat unit are 4.923(2)–4.966(2) Å. The approximate dimensions of the oval-shaped cavity are approximately

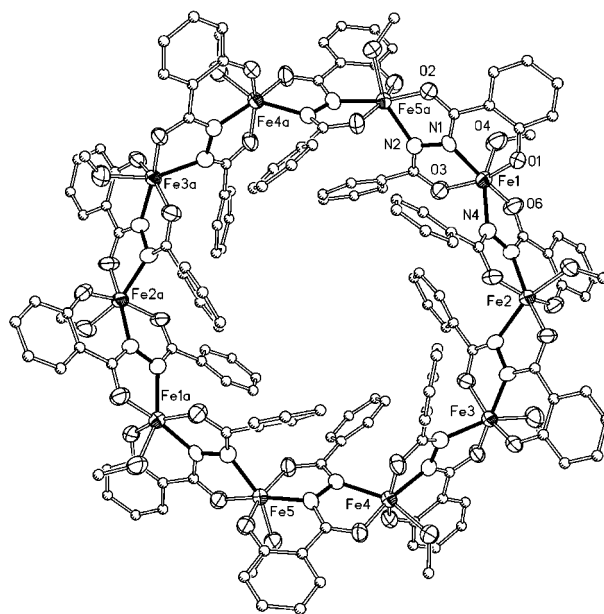


Figure 2. Perspective view of **3** (solvent molecules and all hydrogen atoms have been omitted for clarity). Selected bond lengths [Å] and angles [°]: Fe1–O1 1.936(8), Fe1–O3 2.012(8), Fe1–O6 1.984(8), Fe1–N1 2.073(9), Fe1–O4 2.142(9), Fe1–N4 2.183(9); O1–Fe1–O3 161.6(3), O3–Fe1–N1 75.6(3), O3–Fe1–O6 96.2(3), O1–Fe1–O4 91.1(4), N1–Fe1–O4 86.2(3), O1–Fe1–N4 90.4(3), N1–Fe1–N4 118.4(4), O4–Fe1–N4 155.3(4), O1–Fe1–N1 86.3(3), O1–Fe1–O6 102.2(4), N1–Fe1–O6 163.5(3), O3–Fe1–O4 91.1(4), O6–Fe1–O4 79.6(3), O3–Fe1–N4 95.2(3), O6–Fe1–N4 76.0(3); average neighbor Fe...Fe distance 4.946(2), average near-neighbor Fe...Fe distance 9.315(2); Fe...Fe...Fe 138.92–141.84.

5.70 Å in diameter at the entrance, approximately 13.67 Å (less 1.24 Å for the van der Waals radii of the iron atom) at its largest diameter at the center of the cavity, and approximately 4.16 Å in depth.

All the iron atoms of the ring adopt a distorted octahedron coordination geometry of the FeN_2O_4 type. Compared with the MnN_2O_4 octahedron, there is no Jahn–Teller distortion in the FeN_2O_4 octahedron of compound **3**, owing to the d^5 high-spin electronic configuration of the iron(III) ion.

Several [9]metallacrown-3 compounds^[3,4] and a [15]metallacrown-5^[9b] have the metal centers of the ring in a propeller configuration and with the same chiralities. The manganese and iron atoms in the [30]azametallacrown-10 compounds **2** and **3** exhibit a propeller configuration; however, the chiralities of the ten manganese/iron atoms in the two compounds alternate between the Δ and Λ forms.^[13] In each azametallacrown, five methanol groups coordinated to the metal centers with Δ configuration are found on one face of the azametallacrown, and the remaining five methanol groups coordinated to the other metal centers with Λ configuration are found on the other face of the azametallacrown. The two faces of each azametallacrown have opposite chiralities.

The planar decanuclear structures in the [30]azametallacrowns-10 **2** and **3** are quite different from the planar hexanuclear structures in several [18]metallacrowns-6.^[14] The average M...M...M interatomic angles in the 30-membered core ring of **2** and **3** are 138.87° and 140.67°, respectively. These values are close to the interior angle of 144° in an n -decagon. However, the average M...M...M

angles in the [18]metallacrowns-6 are $116.89(2)^\circ$ for $[\text{Mn}_6(\text{C}_8\text{H}_6\text{N}_3\text{O}_2\text{S})_6(\text{CH}_3\text{OH})_6] \cdot 11.5\text{CH}_3\text{OH}$, and $118.16(4)^\circ$ for $[\text{Fe}_6(\text{C}_8\text{H}_6\text{N}_3\text{O}_2\text{S})_6(\text{CH}_3\text{OH})_6] \cdot 12\text{CH}_3\text{OH} \cdot 2\text{H}_2\text{O}$,^[14] which are close to the ideal internal angle of 120° in an *n*-hexagon. The change in the ring size between the [30]metallacrowns-10 and the [18]metallacrowns-6 is probably caused by the steric interactions between the bridging multidentate ligands in the different metallacrowns.

The magnetic behavior of **2** is illustrated in Figure 3. The molar effective magnetic moment (μ_{eff}) decreases slightly with decreasing temperature from $14.73 \mu_{\text{B}}$ at 275 K to $13.32 \mu_{\text{B}}$ at 60 K. Below 60 K, μ_{eff} decreases rapidly and reaches $4.38 \mu_{\text{B}}$ at 4 K. Even at 275 K, the μ_{eff} value is smaller than the value of the sum expected for ten discrete paramagnetic systems with $S = 2$ ($\mu_{\text{eff}} = 15.18 \mu_{\text{B}}$). This is characteristic of antiferromag-

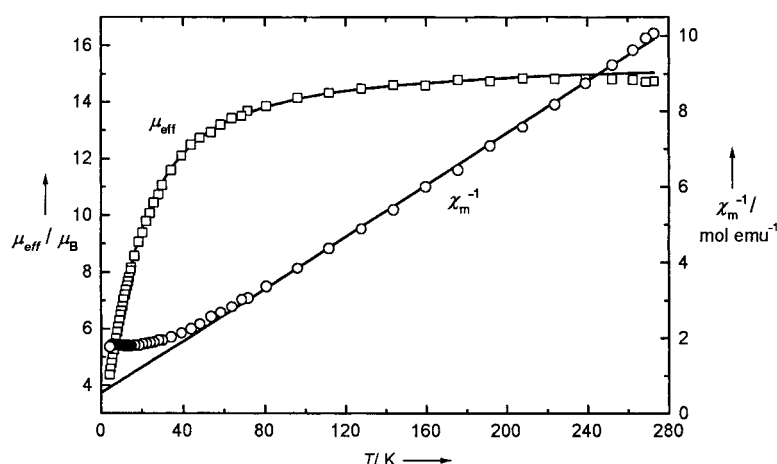


Figure 3. The effective magnetic moment (μ_{eff}) and the inverse susceptibility χ_m^{-1} data as a function of temperature for **2**. Open points represent observed results, and solid lines for χ_m^{-1} and μ_{eff} represent the fitting curves based on the Curie–Weiss law and on a simplified exchange fit as described in the text, respectively.

netic coupling, which is further suggested by a negative Weiss constant ($\theta = -16.0(1) \text{ K}$) using the data within $T > 63 \text{ K}$. Based on irreducible tensor operators^[15] with the Hamiltonian operator given as $H = -\sum_{ij} J_{ij} S_i S_j$, one can get the energy of 856945 spin states arising from the coupling of the 10 $S = 2$ centers. Nevertheless, because of the different S values ranging from 0 to 20, the dimensions of the Hamiltonian matrices are too big for a true fitting procedure, even when taking the inverse center symmetry into account. Therefore, a simplified set of parameters for magnetic interactions were tested to analyze the magnetic properties quantitatively. Exchanges propagated between the neighboring centers (J_1), and between the near-neighboring centers (J_2) were considered. The distances between the paramagnetic centers in other positions are greater than $12.749(2) \text{ \AA}$. Consequently, their interactions are weak and negligible. A least-squares fit for all the data gives rise to the parameters $J_1/k = -1.275(2) \text{ K}$, $J_2/k = -0.73(3) \text{ K}$, and the agreement factor $F = \sum[(\chi_{\text{obs}} - \chi_{\text{calc}})^2 / \chi_{\text{obs}}] = 7.893 \times 10^{-3}$. The negative values of J denote antiferromagnetic coupling between the manganese(III) centers. As expected, the interactions between neighboring centers dominate the others that are derived

from the absolute values of J_1 and J_2 . The antiferromagnetic nature of the interactions can be understood in terms of an overlap, through the bridging group, between the singly occupied metal d orbitals. Furthermore, Mn^{3+} in an elongated octahedral geometry exhibits magnetic anisotropy due to the zero-field splitting (ZFS), but the system is too complex to include the ZFS in magnetic analysis.

In summary, the manganese(III) and iron(III) [30]azametallacrown-10 compounds **2** and **3** expand the ring size of known metallacrown clusters from [9]metallacrown-3 to a 30-membered ring system. All the metal atoms in the rings of **2** and **3** adopt a propeller configuration, and have alternating Δ/Δ stereochemistries. The manganese azametallacrown molecules show large magnetic moments and have a remarkable toroid-like shape with a relatively large internal cavity. Hence it is possible that such molecules may act as a scaffold for the formation of supermolecules by guest binding within the cavity. It may also suggest a new approach for developing magnetic materials.

Experimental Section

1: Benzoyl chloride (5.55 g, 39.5 mmol) was added to a solution of sodium benzoate (5.688 g, 39.5 mmol) in chloroform (60 mL) at 5°C . The reaction mixture was slowly warmed to 22°C , stirred for 2 h, and then filtered. Salicylhydrazide (5.00 g, 32.9 mmol) was added to the filtrate to give a white suspension, which was collected and rinsed with chloroform and diethyl ether. Yield: 8.200 g, 95.0%, m.p. 255°C .

2: A mixture of $[\text{Mn}(\text{acetylacetonate})_2]$ (35 mg, 0.1 mmol) in methanol (15 mL) and *N*-phenylsalicylhydrazidate (25 mg, 0.1 mmol) in chloroform (15 mL) was stirred for 15 min. The resulting dark brown solution was filtered. After standing for six days, dark brown rectangular crystals were obtained from the filtrate. Compound **2** is air-sensitive. Elemental analysis: $\text{C}_{171}\text{H}_{206}\text{Cl}_{10}\text{Mn}_{10}\text{N}_{20}\text{O}_{57}$ (%): calcd: C 47.1, H 4.8, N 6.4, O 20.9; found: C 46.6, H 4.4, N 6.8, O 21.3.

3: A mixture of $\text{Fe}(\text{OAc})_3$ (46.6 mg, 0.2 mmol) in methanol (15 mL) and *N*-phenylsalicylhydrazidate (51.4 mg, 0.2 mmol) in chloroform (15 mL) was stirred for 15 min. The resulting dark violet-red solution was filtered. After standing for seven days, black-brown rhombohedral crystals were separated from the filtrate. Compound **3** is air-sensitive. Elemental analysis: $\text{C}_{165.5}\text{H}_{196}\text{Cl}_6\text{Fe}_{10}\text{N}_{20}\text{O}_{57.5}$ (%): calcd: C 47.8, H 4.8, N 6.7, O 22.1; found: C 47.2, H 4.4, N 7.1, O 22.5.

Crystals of compounds **2** and **3** were mounted in a glass capillary with the mother liquor to prevent the loss of the structural solvents during X-ray diffraction data collection. The data were recorded on a Siemens Smart CCD area detector diffractometer with graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), the scan mode being ω . Programs used: Data correction: SMART (Siemens, 1996), cell refinement: SAINT (Siemens, 1996), and data reduction: SAINT (Siemens, 1996). The structures were solved by direct methods using SHELXS-86 and refined by full-matrix least-squares calculations with SHELXL-97. All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms on the benzene ring in **2** and **3** were located at calculated positions ($\text{C}–\text{H} = 0.93 \text{ \AA}$) with isotropic displacement parameters set to $1.2 U_{\text{eq}}(\text{C})$. Some of the other hydrogen atoms in **2** were located at calculated positions and/or at the positions found from a difference Fourier map. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-148152 (**2**) and CCDC-148153 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Crystal data for **2** ($C_{171}H_{206}Cl_{10}Mn_{10}N_{20}O_{57}$): $M_r = 4357.46$, dark brown crystal ($0.35 \times 0.40 \times 0.55$ mm), triclinic, space group $P\bar{1}$, $a = 14.5331(2)$, $b = 18.1704(1)$, $c = 21.3923(2)$ Å, $\alpha = 76.545(1)$, $\beta = 74.220(1)$, $\gamma = 86.025(1)$, $V = 5287.03(9)$ Å³, $Z = 1$, $T = 293(2)$ K, $\rho_{\text{calc}} = 1.369$ g cm⁻³, $F(000) = 2248$, $\mu = 0.782$ mm⁻¹. Of the 28654 reflections ($(2\theta)_{\text{max}} = 50.14^\circ$), 18480 unique reflections were collected. From these, 9215 reflections with $I > 2\sigma(I)$ were used to solve the structure and were refined on F^2 by full-matrix least-squares techniques (SHELXL-97). At convergence, $R_1 = 0.0834$ and the goodness-of-fit on F^2 is 1.121. The maximum and minimum residual peaks on the final difference Fourier map were 0.934 and -0.879 e Å⁻³, respectively.

Crystal data for **3** ($C_{165.5}H_{196}Cl_6Fe_{10}N_{20}O_{57.5}$): $M_r = 4156.62$, black-brown crystal ($0.34 \times 0.35 \times 0.72$ mm), triclinic, space group $P\bar{1}$, $a = 14.7040(4)$, $b = 18.9081(5)$, $c = 21.0783(5)$ Å, $\alpha = 71.201(1)$, $\beta = 77.076(1)$, $\gamma = 84.757(1)$, $V = 5406.0(2)$ Å³, $Z = 1$, $T = 293(2)$ K, $\rho_{\text{calc}} = 1.277$ g cm⁻³, $F(000) = 2151$, $\mu = 0.800$ mm⁻¹. Of the 23991 reflections ($(2\theta)_{\text{max}} = 47.10^\circ$), 14784 unique reflections were collected. From these, 7372 reflections with $I > 2\sigma(I)$ were used to solve the structure and were refined on F^2 by full-matrix least-squares techniques (SHELXL-97). At convergence, $R_1 = 0.0945$ and the goodness-of-fit on F^2 is 1.017. The maximum and minimum residual peaks on the final difference Fourier map were 0.893 and -0.455 e Å⁻³, respectively.

The magnetic susceptibility data were obtained by using a Quantum Design PPMS 6000 magnetometer in the temperature range from 4 to 275 K at an applied magnetic field of 10 KG; whereby the diamagnetic contributions were estimated from Pascal's constants.

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Coordination Chemistry in the Solid: Study of the Incorporation of Cu^{II} into Cyclam-Containing Hybrid Materials

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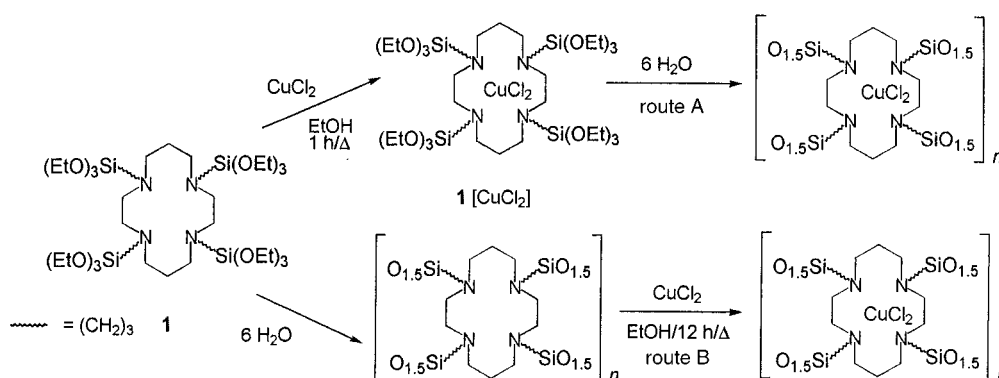
Nanostructured organic–inorganic hybrid materials have known a considerable expansion in the past decade,^[1–5] because they may provide unique combinations of properties which cannot be obtained by other ways. Among the possibilities offered by this class of solids, the preparation of materials able to strongly chelate metal cations which could remain chemically accessible seemed to us to be of great interest. Indeed, such materials could be interesting to study the coordination chemistry within the solid state as well as for their potential applications in catalysis,^[6] separations,^[7] optical devices,^[8] or magnetic properties for example. Such applications require the incorporation within the materials of a good chelating ligand. Saturated polyazamacrocycles and especially 1,4,8,11-tetraazacyclotetradecane^[9–11] (cyclam) having attracted much attention because of their remarkable binding ability towards transition and heavy metal cations, we set out to prepare hybrid materials incorporating cyclam moieties by using the sol–gel process.

We have shown that nanostructured materials are kinetically controlled.^[3, 4, 12] The texture of the solids is highly dependent on all the parameters able to modify the kinetics of polycondensation (catalyst,^[13] concentration of the reagent,^[13] solvent,^[13] temperature,^[13a] and the organic spacer^[13]). Furthermore, the importance of the organic moiety in the arrangement of solids obtained by the sol–gel process was displayed, giving rise to a possible short-range organization.^[3, 4, 14, 15] In this context, it seemed interesting to investigate the incorporation of metal salts into cyclam-containing hybrid materials by two routes: the hydrolysis and polycondensation of metal salt/silylated cyclam derivatives complexes (Scheme 1, route A) or by hydrolysis and polycondensation of silylated cyclam derivatives followed by the direct incorporation of metal salts into the xerogels (Scheme 1, route B).

We have shown that the hydrolysis and polycondensation of silylated cyclam Cu^{II} and Co^{II} complexes (route A, Scheme 1) gives rise quantitatively to hybrid materials incorporating the Cu^{II} and Co^{II} salts,^[16] thus the complexation of metal cations survives the sol–gel process. Herein we describe the direct incorporation of CuCl₂ into hybrid materials (route B). By using X-ray fluorescence and ESR spectroscopy, we show that the two routes of incorporation of the salts are not equivalent

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Scheme 1.

and that the coordination chemistry within the solids and in solution are remarkably different.

The sol–gel polycondensation of **1**^[16] gave rise to xerogels **X1–X3** the texture of which depends on the experimental conditions (Table 1). Hydrolysis and polycondensation of the

Table 1. Texture data of the xerogels prepared from **1** or **1**[CuCl₂] in EtOH and in the presence of tetrabutylammonium fluoride (TBAF) 1% as the catalyst.

Precursor	<i>T</i> [°C]	Xerogel	<i>S</i> _{BET} [m ² g ^{−1}] ^[a]	Mean pore <i>d</i> [Å] ^[b]
1	24 ^[c]	X1	< 10	–
1	24	X2	370	< 30
1	110	X3	800	20–50
1 [CuCl ₂]	22	X [CuCl ₂] 1A ^[d]	< 10	–
1 [CuCl ₂]	22	X [CuCl ₂] 1B	< 10	–

[a] Measured according to the Brunauer–Emmett–Teller (BET) method.

[b] Measured according to the Barret–Joyner–Halenda (BJH) method; *d* = diameter. [c] No catalyst. [d] THF as solvent.

complex **1**[CuCl₂] (route A) was also achieved leading to xerogels which were named as indicated in Table 1. The total amount of incorporated copper within the hybrid materials according to the route A was measured by X-ray fluorescence spectroscopy (Table 2). As the number of cyclam moieties per gram of solid was inferred from elemental analysis of the material (% of nitrogen), it was possible to calculate the

Table 2. Amount of copper incorporated into the xerogels prepared by route A.

Xerogel	[Cu] _{total} [mmol g ^{−1}] ^[a]	[Cyclam] [mmol g ^{−1}] ^[b]	Metalated sites [% (±3)]	[Cu ^{II}] _{ESR} [mmol g ^{−1}]	[Cu ^{II}] _{ESR} / [Cu] _{total} [%]
X [CuCl ₂] 1A	0.95	0.97	98	0.79	83
X [CuCl ₂] 1B	0.97	0.97	100	0.80	82

[a] Measured by X-ray fluorescence spectroscopy. [b] Inferred from nitrogen elemental analysis.

percentage of sites metalated for each solid. Thus, as indicated in Table 2, the metal cations were quantitatively retained within the xerogels.

An alternative method using ESR spectroscopy was devised to quantify the amount of Cu^{II} within the materials.^[17] The calibration was done with Cu^{II}–cyclam complexes diluted to different concentrations (0.2–1 mmol g^{−1}) into silica. As indicated in Table 2, the amount of Cu^{II} ions measured by this

method for materials prepared by route A is slightly lower than the total amount of copper found by X-ray fluorescence. That can be attributed to the standardization of the apparatus. Thus, it can be concluded that both the methods are in good agreement.

Let us now consider the direct incorporation of CuCl₂ into xerogels **X1–X3** prepared from **1** (route B, Scheme 1). After reaction,

the xerogels were described as indicated in Table 3. The total amount of cation within the hybrid materials was first measured by X-ray fluorescence spectroscopy. From these results, it appears that the incorporation of CuCl₂ was quantitative (that is, 1 Cu^{II} per cyclam moiety) when the xerogels were treated with two equivalents of salts (Table 3 entries 1, 3, 5). When the xerogels were treated with one equivalent of salt (entries 2, 4, 6) or with less than one equivalent of salt (entry 7) the cation uptake was quite significant, in comparison to the amount of salt added. Thus, these results show that all the chelating sites of the materials are accessible under mild experimental conditions. Noteworthy is that the cation binding ability of the materials obtained by hydrolysis and polycondensation of dibenzo-[18]crown-6 ethers derivatives bearing four hydrolyzable Si(OR)₃ groups was quite different:^[18] about 45% of crown ether sites are not accessible to K⁺ or Na⁺ ions. The better cation-binding ability of cyclam moieties is because of the high stability of copper–cyclam complexes^[19] but also to the flexibility of tetraazamacrocycles even within the solid. Furthermore, a large surface area is not necessary for the complexation as, for example, the complexation was quantitative for both materials **X3** (entry 5, Table 3) with *S*_{BET} = 800 m² g^{−1}, and **X1** (entry 1, Table 3) with *S*_{BET} < 10 m² g^{−1}. This result is also explained by the flexibility of the cyclam moieties which allows an easy penetration and diffusion of the reagents into the materials.^[20, 21]

Surprisingly, from all the materials prepared by route B, the amount of Cu^{II} measured by ESR spectroscopy (Table 3) appears notably lower than the total amount of Cu titrated by X-ray fluorescence. Furthermore, it is worth noting that the gap between the X-ray fluorescence and ESR measurements decreases as the amount of incorporated salt (compare in Table 3, entries 1 and 2; 3 and 4; 5 and 6) decreases.

We think that the discrepancy between the amount of Cu^{II} found from ESR measurements and the total amount of Cu titrated by X-ray fluorescence is because of the proximity of metal centers allowing the formation of antiferromagnetic Cu–Cu interactions^[22–26] and thus leading to a lower intensity of the ESR signal at 3200 G.

As ESR spectroscopy is a convenient technique to study metal–metal interactions,^[22–26] we recorded, at 100 K, the X-band ESR spectra of materials containing copper salts introduced by the two routes. The ESR spectrum of the

Table 3. Amount of copper incorporated into the xerogels prepared by route B.

Entry	Starting xerogel	[Cyclam] [mmol g ⁻¹] ^[a]	CuCl ₂ ^[b]	Xerogel after reaction	[Cu] _{total} [mmol g ⁻¹] ^[c]	Metalated sites [% (±3)]	[Cu ^{II}] _{ESR} [mmol g ⁻¹]	$\frac{[\text{Cu}^{\text{II}}]_{\text{ESR}}}{[\text{Cu}]_{\text{total}}}$ [%]
1	X1	1.27	2	X1 [2 CuCl ₂]	1.31	103	0.34	26
2	X1	1.27	1	X1 [1 CuCl ₂]	0.95	75	0.37	39
3	X2	1.28	2	X2 [2 CuCl ₂]	1.32	103	0.16	12
4	X2	1.28	1	X2 [1 CuCl ₂]	1.02	80	0.35	34
5	X3	1.33	2	X3 [2 CuCl ₂]	1.33	100	0.15	11
6	X3	1.33	1	X3 [1 CuCl ₂]	0.95	71	0.22	23
7	X3	1.33	0.5	X3 [0.5 CuCl ₂]	0.56	42	0.20	36

[a] Inferred from nitrogen elemental analysis. [b] Number of equivalents. [c] Measured by X-ray fluorescence spectroscopy.

material **X**[CuCl₂]**1A** (route A) exhibits a strong absorption at 3200 G ($g \cong 2.15$) characteristic for Cu^{II} centers and no signal at lower field (Figure 1 a and c). In contrast, the ESR

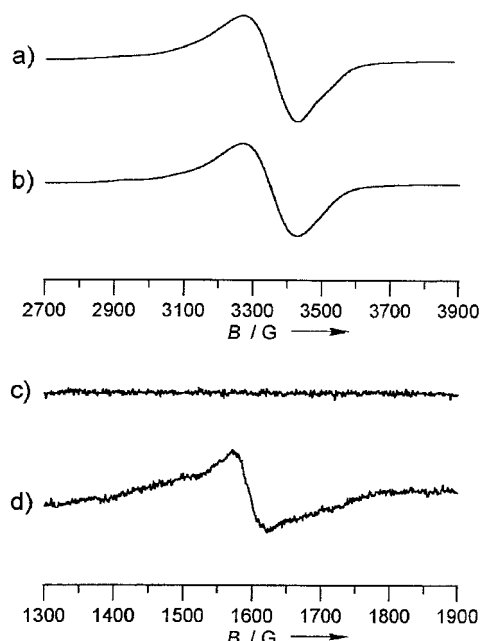


Figure 1. X-band ESR spectra recorded at 100 K of the allowed transitions for a) **X**[CuCl₂]**1A**, b) **X3**[1 CuCl₂], and of the half-field transitions for c) **X**[CuCl₂]**1A**, d) **X3**[1 CuCl₂].

spectrum of the material **X3**[1 CuCl₂] (route B) displays not only the signal at ≈ 3200 G but also a weak absorption at 1550 G ($g \cong 4.40$; Figure 1 b and d). The absorption at ≈ 3200 G was assigned to the allowed transition ($\Delta M_s = 1$) while the weaker one can be attributed to a forbidden transition^[22–26] ($\Delta M_s = 2$) which is characteristic of dicopper interactions and attests to a dipolar exchange between two copper units. This phenomenon has been observed from the solution ESR spectra of dinuclear Cu^{II} complexes in which two cyclam rings are in a face-to-face conformation,^[24] and was also observed from the solution ESR spectra of face-to-face dicopper bisporphyrin complexes^[26] and of dinitroxyl radicals.^[25] This observation suggests that during the sol–gel process of materials prepared by route B, the cyclam moieties arrange in such a way that two complexed copper ions are in an analogous situation to that in macrotricyclic ligands^[24] designed for the study of metal–metal interactions. This conformation explains the difference between the total amount of copper determined from titration by X-ray

fluorescence and the amount of Cu^{II} determined by ESR spectroscopy. It is worth noting that short-range organization in hybrid organic–inorganic materials has been observed.^[3] In contrast, the arrangement of the solids prepared by route A does not give rise to such dinuclear species, as revealed by ESR spectra, and therefore there is a good agreement between the results of both the methods of titration of the copper in these materials.

This study describes two routes for the incorporation of copper salts within cyclam-containing hybrid materials, however, the routes are not equivalent. The incorporation of Cu^{II} centers into materials by route B gives rise to Cu–Cu interactions which are not observed when the metal centers are introduced by route A. These differences are probably because of the nature of the precursor material which has not the same flexibility in both cases. The precursor material in route B is a flexible cyclam derivative while the precursor material of route A is a more rigid copper–cyclam complex (Scheme 1). Thus, the results suggest a coordination chemistry in the solid state which is not a copy of that in solution as it depends on the solid organization.

Experimental Section

The ESR spectra were recorded in the solid state on a Bruker ESP 300 spectrometer at X-band (9.6 GHz), from the Centre de Spectrométrie Moléculaire de l'Université de Bourgogne, equipped with a double cavity and a liquid nitrogen cooling accessory. The X-Ray fluorescence measurements were performed on a Oxford Lab-X 3000.

Incorporation of CuCl₂ by route B: The direct incorporation of CuCl₂ into the xerogels **X1**–**X3** was carried out as follows: xerogels **X1**–**X3** (500 mg) were stirred under reflux for 12 h in an ethanol (20 mL) solution of CuCl₂ (0.5, 1, or 2 equiv). The reaction mixture was then filtered and washed four times with ethanol. The resulting powder was dried at 120 °C under 20 mm Hg for 12 h and the xerogels were described as indicated in Table 3.

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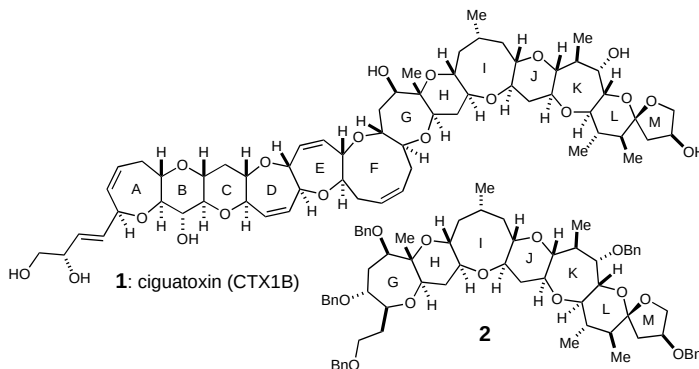
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Synthetic Studies on Ciguatoxin: A Highly Convergent Synthesis of the GHIJKLM Ring System Based on *B*-Alkyl Suzuki Coupling

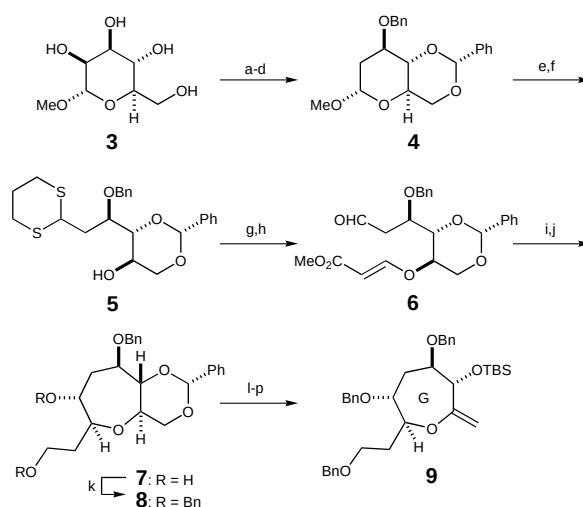
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Ciguatoxin (CTX1B, **1**) and its congeners, naturally occurring polycyclic ethers originating from marine unicellular algae, are the principal toxins associated with ciguatera fish poisoning.^[1, 2] These potent neurotoxins reportedly bind to the same site of voltage-sensitive sodium channels as brevetoxins, another class of structurally related marine toxins.^[3] Their structural complexity and exceptionally potent neurotoxicity, as well as their limited availability from natural sources, have attracted the interest of synthetic chemists, and a number of

synthetic studies by us^[4] and others^[5, 6] have been reported. Recently, we developed a powerful strategy for the convergent assembly of a polyether structure based on *B*-alkyl Suzuki coupling.^[7–9] Here we describe the application of this strategy to a more highly functionalized system, which led to a convergent synthesis of the GHIJKLM ring fragment **2** of ciguatoxin.



Synthesis of exo-olefin **9**, corresponding to the G ring, started with methyl α -D-mannopyranoside (**3**), which was converted into **4** by a four-step sequence including benzylidene acetal formation, regioselective tin-mediated benzylation of the equatorial alcohol,^[10] and Barton deoxygenation of the remaining hydroxy group^[11] (Scheme 1). Compound **4** was treated with 1,3-propanedithiol in the presence of concen-



Scheme 1. Synthesis of the G ring exo-olefin **9**. a) $\text{PhCH}(\text{OMe})_2$, CSA, DMF, RT; b) $n\text{Bu}_2\text{SnO}$, benzene, reflux, then CsF, BnBr, DMF, RT; c) NaH, CS_2 , MeI, THF, RT; d) $n\text{Bu}_3\text{SnH}$, AIBN, benzene, reflux, 24 % (4 steps); e) $\text{HS}(\text{CH}_2)_3\text{SH}$, conc. HCl, CHCl_3 , RT; f) $\text{PhCH}(\text{OMe})_2$, CSA, CH_2Cl_2 , RT, 46 % (2 steps); g) methyl propiolate, NMM, CH_2Cl_2 , RT, 97 %; h) MeI, NaHCO_3 , $\text{MeCN}/\text{H}_2\text{O}$, RT, 98 %; i) SmI_2 , MeOH, THF/HMPA, 0 °C; j) LiAlH_4 , THF, RT, 72 % (2 steps); k) NaH, BnBr, DMF, RT, 84 %; l) CSA, MeOH, RT, 89 %; m) TBSOTf, 2,6-lutidine, CH_2Cl_2 , RT; n) CSA, MeOH, 0 °C, 89 % (2 steps); o) I_2 , PPh_3 , imidazole, THF, RT; p) $t\text{BuOK}$, THF, RT, 85 % (2 steps). AIBN = 2,2'-azobisisobutyronitrile, Bn = benzyl, CSA = camphorsulfonic acid, DMF = *N,N*-dimethylformamide, HMPA = hexamethylphosphoric triamide, NMM = *N*-methylmorpholine, OTf = trifluoromethanesulfonate, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

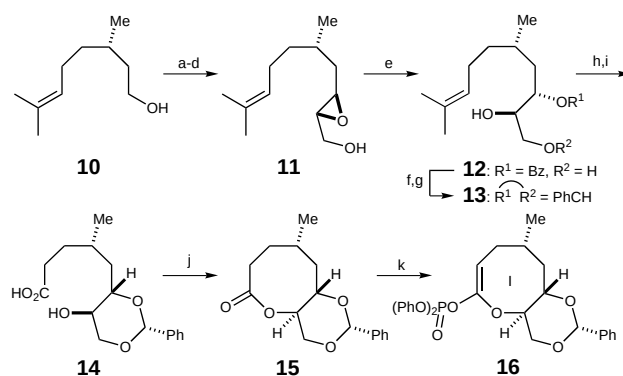
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trated HCl, and the resulting dithiane triol was protected as the benzylidene acetal **5**. Alcohol **5** was converted to the corresponding β -alkoxyacrylate, which on treatment with methyl iodide gave aldehyde **6** in 95% yield for the two steps. SmI_2 -mediated reductive cyclization^[12] of **6** in the presence of HMPA led to stereoselective formation of a seven-membered ether ring. Reduction of the unpurified product thus obtained with LiAlH_4 provided diol **7** as a single isomer in 72% yield for the two steps, which was then benzylated to give **8**. Removal of the benzylidene acetal was followed by silylation to give a bis-silyl ether. Selective removal of the primary TBS group followed by iodination of the resulting alcohol and subsequent treatment with a base completed the synthesis of the desired exo-olefin **9** (56% overall yield from **7**).

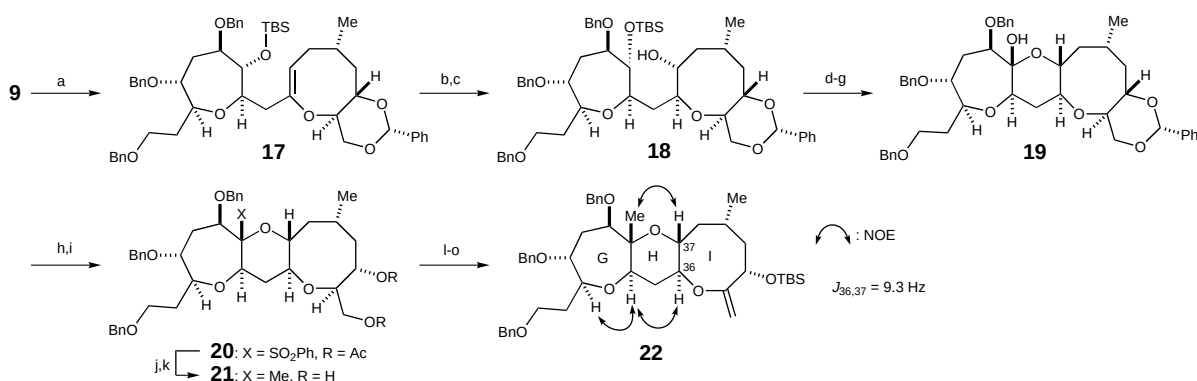
Construction of enol phosphate **16**, representing the I ring, began with (*S*)-(-)-citronellol (**10**; Scheme 2). Oxidation with $\text{SO}_3 \cdot \text{pyridine}$ followed by Wittig reaction gave the homologated α,β -unsaturated ester, which was subjected to DIBALH reduction and subsequent asymmetric epoxidation to afford epoxy alcohol **11** in 79% overall yield. Regioselective opening of the epoxide ring with ammonium benzoate and $\text{Ti}(\text{O}i\text{Pr})_4$ ^[13] gave 1,2-diol **12** in 70% yield as the only isomer detectable by ^1H NMR spectroscopy (500 MHz). Methanolysis of the benzoyl group followed by selective protection of the 1,3-diol as the benzylidene acetal yielded alcohol **13** in 49% yield for the two steps. Oxidative cleavage of the double bond and subsequent oxidation of the resultant aldehyde with sodium chlorite provided hydroxy acid **14** in 66% overall yield. Lactonization of **14** under Yamaguchi conditions^[14] gave eight-membered lactone **15** (83%), which was readily converted into enol phosphate **16** by the procedure of Nicolaou et al.^[15]

Hydroboration of **9** with 9-BBN and treatment of the resultant alkylborane with enol phosphate **16** under the previously reported conditions^[7b] afforded cross-coupled product **17** in high yield (Scheme 3). Hydroboration of **17** with $\text{BH}_3 \cdot \text{THF}$ under various conditions provided the desired alcohol **18** in only low yield, presumably due to the steric



Scheme 2. Synthesis of the I ring enol phosphate **16**. a) $\text{SO}_3 \cdot \text{pyridine}$, Et_3N , CH_2Cl_2 , DMSO, 0°C ; b) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$, benzene, RT; c) DIBALH, CH_2Cl_2 , -78°C , 86% (3 steps); d) *t*BuOOH, (–)-DET, $\text{Ti}(\text{O}i\text{Pr})_4$, 4-Å molecular sieves, CH_2Cl_2 , -20°C , 92%; e) PhCO_2NH_4 , $\text{Ti}(\text{O}i\text{Pr})_4$, CH_2Cl_2 , RT, then 5% aqueous H_2SO_4 , 70%; f) KOH, MeOH, RT, 81%; g) $\text{PhCH}(\text{OMe})_2$, CSA, CH_2Cl_2 , RT, 61%; h) OsO_4 , NMO, acetone/ H_2O , RT, then NaIO_4 , 70%; i) NaClO_2 , KH_2PO_4 , 2-methyl-2-butene, *t*BuOH/ H_2O , RT, 95%; j) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, then DMAP, benzene, reflux, 83%; k) KHMDS, $(\text{PhO})_2\text{P}(\text{O})\text{Cl}$, THF/HMPA, -78°C , 95%. DMSO = dimethyl sulfoxide, DIBALH = diisobutylaluminum hydride, DET = diethyl tartrate, DMAP = 4-dimethylaminopyridine, KHMDS = potassium hexamethyldisilazide, NMO = *N*-methylmorpholine *N*-oxide.

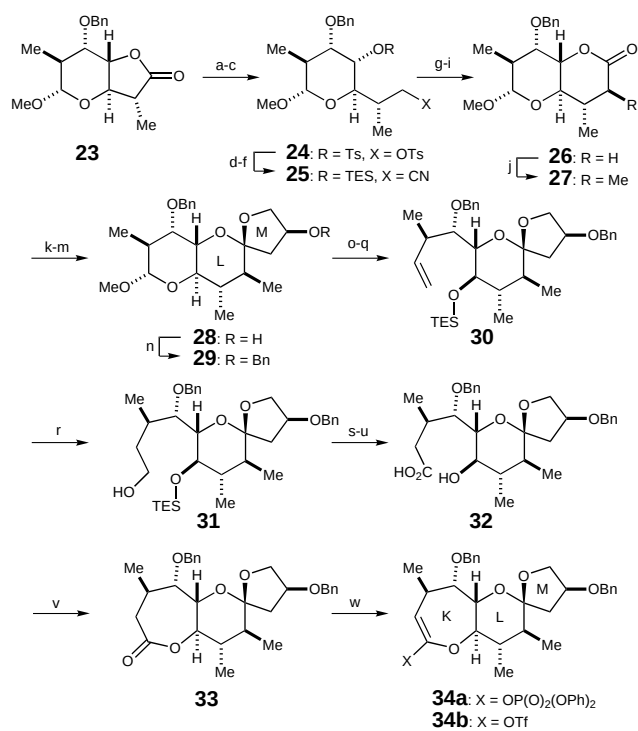
hindrance of the methyl group on the eight-membered ring. We eventually solved the problem in the following manner: Epoxidation of **17** with 3,3-dimethyldioxirane^[16] proceeded stereoselectively to yield the corresponding α -epoxide, which was immediately reduced with Et_3SiH in the presence of $\text{BH}_3 \cdot \text{THF}$ to deliver **18** as the only isolable product in 60% yield for the two steps. Protection of the secondary alcohol as the *p*-methoxybenzyl ether, desilylation followed by oxidation of the resultant alcohol with TPAP/NMO^[17] and oxidative removal of the PMB group with DDQ provided hemiketal **19** as a single stereoisomer. Exposure of **19** to EtSH and $\text{Zn}(\text{OTf})_2$ effected formation of the mixed thioketal and removal of the benzylidene group to give a diol. In situ acetylation of the diol was followed by thiol oxidation to yield



Scheme 3. Synthesis of the GHI ring system **22**. a) 9-BBN, THF, RT, then 1M aqueous NaHCO_3 , **16**, $[\text{Pd}(\text{PPh}_3)_4]$, DMF, 50°C , 85% based on **16**; b) DMDO, acetone, $-78 \rightarrow -20^\circ\text{C}$; c) Et_3SiH , $\text{BH}_3 \cdot \text{THF}$, CH_2Cl_2 , -20°C , 60% (2 steps); d) *t*BuOK, PMBCl, *n*Bu₄NI, THF, RT, 80%; e) TBAF, THF, RT, 97%; f) TPAP, NMO, 4-Å molecular sieves, CH_2Cl_2 , RT, quant.; g) DDQ, $\text{CH}_2\text{Cl}_2/\text{pH 7 phosphate buffer}$ (10/1), RT; h) EtSH , $\text{Zn}(\text{OTf})_2$, CH_2Cl_2 , RT, then Ac_2O , DMAP, Et_3N , 0°C , 84% (3 steps); i) *m*CPBA, CH_2Cl_2 , RT, 96%; j) Me_3Al , CH_2Cl_2 , $-78 \rightarrow 0^\circ\text{C}$; k) K_2CO_3 , MeOH, RT, 83% (2 steps); l) TBSOTf, 2,6-lutidine, CH_2Cl_2 , RT; m) CSA, MeOH/ CH_2Cl_2 (1/1), 0°C , 84% (2 steps); n) I_2 , PPh₃, imidazole, THF, RT, 94%; o) *t*BuOK, THF, 0°C , 87%. 9-BBN = 9-borabicyclononane, DDQ = 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone, DMDO = 3,3-dimethyldioxirane, *m*CPBA = *m*-chloroperbenzoic acid, PMB = *p*-methoxybenzyl, TBAF = tetra-*n*-butylammonium fluoride, TPAP = tetrapropylammonium perruthenate.

sulfone **20** in 62 % overall yield from **18**. Reaction of **20** with Me_3Al ^[7d, 18] provided the desired methylated compound along with the product of its monoacetylation at the primary position. Methanolysis of this mixture gave diol **21** in 83 % yield for the two steps. Straightforward protecting and functional group manipulations transformed **21** into the requisite exo-olefin **22**. The configuration of **22** was unambiguously determined by the coupling constant $J_{36,37} = 9.3$ Hz and NOE experiments, as shown in Scheme 3.

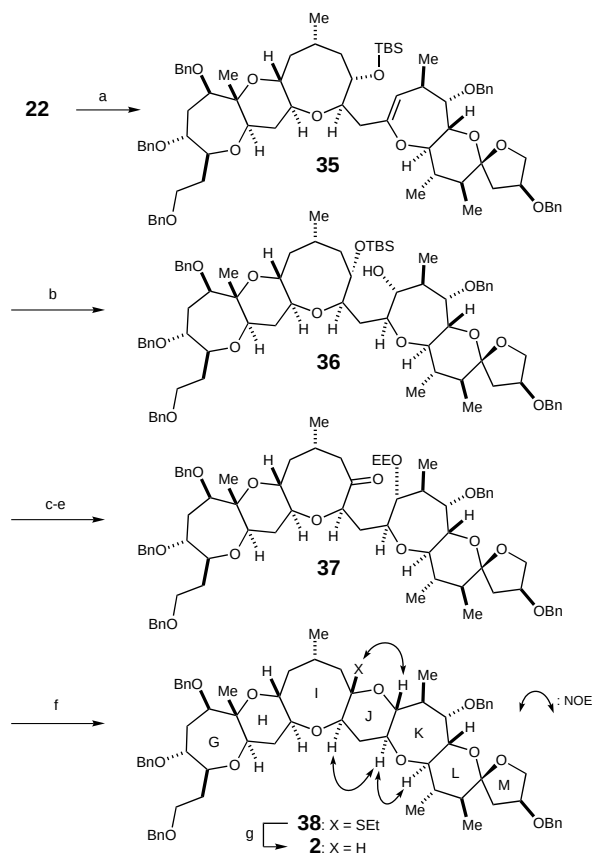
Synthesis of the KLM ring enol phosphate **34a** is summarized in Scheme 4. Bicyclic lactone **23**^[4d] was transformed into nitrile **25** via bis-tosylate **24** in a six-step sequence. Reduction of **25** with DIBALH followed by removal of the TES group with acid gave the corresponding hemiacetal, which was then oxidized with TPAP/NMO to give lactone **26** in 78 % yield for the three steps. Methylation of the lithium enolate derived from **26** led exclusively to methylated lactone **27** in 82 % yield. Construction of the spiroketal M ring was accomplished by asymmetric dihydroxylation with Corey's ligand^[19] by following the previously reported method.^[4d] Treatment of tricyclic



Scheme 4. Synthesis of the KLM ring system **34**. a) DIBALH, CH_2Cl_2 , -78°C ; b) NaBH_4 , MeOH, 0°C ; c) TsCl, Et_3N , DMAP, CH_2Cl_2 , RT, 68 % (3 steps); d) KCN, DMSO, 70°C ; e) Mg, MeOH, RT; f) TESCl, imidazole, DMF, RT, 83 % (3 steps); g) DIBALH, CH_2Cl_2 , -78°C ; h) HOAc/THF/ H_2O , RT; i) TPAP, NMO, 4-Å molecular sieves, CH_2Cl_2 , RT, 78 % (3 steps); j) LiHMDS, MeI, THF, -78°C , 82 %; k) allylmagnesium bromide, THF, -78°C , 68 %; l) OsO_4 , *N,N'*-bis(2,4,6-trimethylbenzyl)-(*S,S'*)-1,2-diphenyl-1,2-diaminoethane, CH_2Cl_2 , -90°C , then aqueous NaHSO_3 , THF, 70°C ; m) CSA, benzene, RT, 79 % (2 steps); n) NaH, BnBr, DMF, RT, 98 %; o) $\text{BF}_3 \cdot \text{OEt}_2$, Me_2S , CH_2Cl_2 , 0°C ; p) $\text{Ph}_3\text{PP}^+\text{CH}_3\text{Br}^-$, NaHMDS, THF, 40°C ; q) TESOTf, 2,6-lutidine, CH_2Cl_2 , RT, 73 % (3 steps); r) 9-BBN, THF, RT $\rightarrow 40^\circ\text{C}$, then 3 M NaOH, 30 % H_2O_2 , RT, 98 %; s) $\text{SO}_3 \cdot \text{pyridine}$, Et_3N , $\text{CH}_2\text{Cl}_2/\text{DMSO}$, 0°C ; t) NaClO_2 , KH_2PO_4 , 2-methyl-2-butene, *t*BuOH/ H_2O , RT; u) 0.5 M HCl, THF, RT, 55 % (3 steps); v) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, then DMAP, benzene, reflux, 93 %; w) KHMDS, $(\text{PhO})_2\text{P}(\text{O})\text{Cl}$ or PhNTf_2 , THF/HMPA, -78°C , 87 % for **34a**, 88 % for **34b**. TES = triethylsilyl, Ts = *p*-toluenesulfonyl.

29 with Me_2S and $\text{BF}_3 \cdot \text{OEt}_2$ ^[20] effected selective cleavage of the methyl acetal portion to give a hemiacetal, which was subjected to Wittig methylenation and protection of the resulting alcohol as the TES ether to give olefin **30** in 73 % overall yield. Hydroboration with 9-BBN followed by oxidative workup provided alcohol **31** (98 %), which was oxidized in a two-step procedure to give, after desilylation, hydroxy acid **32** in 55 % overall yield. Lactonization of **32** according to the Yamaguchi protocol yielded seven-membered lactone **33** (93 %), which could be easily converted to enol phosphate **34a** in 87 % yield.

With the required coupling partners **22** and **34a** in hand, we next investigated the crucial coupling reaction. However, phosphate **34a** proved to be a poor substrate for *B*-alkyl Suzuki coupling. Attempted coupling of the alkylborane derived from **22** with **34a** (aqueous 1 M NaHCO_3 , $[\text{Pd}(\text{PPh}_3)_4]$, DMF, rt $\rightarrow 50^\circ\text{C}$) gave a trace of the desired coupled product **35**, and unconsumed phosphate **34a** could be recovered. After extensive investigation, it was discovered that the crucial *B*-alkyl Suzuki coupling could be accomplished by using the more reactive enol triflate **34b**, which was prepared from **33** (Scheme 4). The alkylborane derived from **22** was coupled in situ with **34b**^[7a] to furnish the desired **35** in 71 % yield based on **34b** (Scheme 5). Hydroboration of **35** with $\text{BH}_3 \cdot \text{THF}$ followed by oxidation led to alcohol **36** as a single stereo-



Scheme 5. Synthesis of the GHIJKLM ring system **2**. a) 9-BBN, THF, RT, then 3 M aqueous Cs_2CO_3 , **34b**, $[\text{Pd}(\text{PPh}_3)_4]$, DMF, 0°C , 71 % based on **34b**; b) $\text{BH}_3 \cdot \text{THF}$, THF, RT, then 3 M NaOH, 30 % H_2O_2 , RT, 81 %; c) EVE, CSA, CH_2Cl_2 , RT; d) TBAF, THF, RT; e) TPAP, NMO, 4-Å molecular sieves, CH_2Cl_2 , RT; f) EtSH, $\text{Zn}(\text{OTf})_2$, CH_2Cl_2 , RT; g) Ph_3SnH , AIBN, toluene, reflux, 56 % (5 steps). EVE = ethyl vinyl ether.

isomer in 81 % yield. Protection as the ethoxyethyl (EE) ether followed by desilylation and oxidation of the resulting alcohol with TPAP/NMO provided ketone **37**. Exposure of **37** to EtSH in the presence of Zn(OTf)₂ gave mixed thioketal **38**. Finally, radical reduction^[18] of **38** furnished the target GHIJKLM ring system **2** in 56 % overall yield from **36**. The configuration of **2** was unambiguously determined by NOE experiments.

In conclusion, we have developed a highly convergent synthetic route to the GHIJKLM ring system **2** of ciguatoxin. The present synthesis demonstrates the general applicability of a strategy based on *B*-alkyl Suzuki coupling to the convergent synthesis of a polyether system. Progress toward the completion of the total synthesis of ciguatoxins is underway.

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Turning On Cell Migration with Electroactive Substrates**

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Herein we describe an electroactive substrate that was designed to turn on the migration of mammalian cells. The migration of cells is important in many developmental and disease processes that are temporally regulated.^[1] Mechanistic studies of cell migration—which depend on specific interactions of cell-surface receptors with ligands of the extracellular matrix^[2]—are complicated by the large number of ligands present in the matrix and the changes in ligand activity over

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time. Studies of cell migration would benefit from model substrates that both define completely the ligand–receptor interactions between substrate and cell and that allow those interactions to be regulated in time. We now report a class of dynamic substrates that can selectively “turn on” ligands under electrical control and induce the migration and proliferation of cells. We use this substrate to demonstrate a new screening assay for the discovery of promigratory and antimigratory compounds.

The dynamic substrate is based on a self-assembled monolayer (SAM) that presents hydroquinone groups on a background of penta(ethylene glycol) groups.^[3, 4] We have shown that the hydroquinone group undergoes oxidation when an electrical potential is applied to the underlying gold film to give the corresponding quinone, which then undergoes a selective and efficient Diels–Alder reaction with cyclopentadiene to afford a covalent adduct.^[5] When the diene is tethered to a ligand, the Diels–Alder reaction results in the immobilization of the ligand on the monolayer.^[6] This strategy therefore provides an electrochemical route to turn on the presentation of immobilized ligands. The penta(ethylene glycol) groups, which comprise the major component of the monolayer, are critical to this design because they prevent the nonspecific adsorption of proteins to the monolayer and

ensure that the interaction of cells with the substrate is mediated by the immobilized ligands alone.^[7]

To create a surface that could be electrically switched from a state that prevented cell attachment (an inert monolayer) to a state that promoted cell attachment, we prepared a monolayer presenting hydroquinone and penta(ethylene glycol) groups in a ratio of 1:99. This monolayer was completely inert to the attachment of cells. Application of an electrical potential of 500 mV (versus Ag/AgCl reference^[8]) for 10 seconds resulted in the oxidation of hydroquinone to quinone, which then reacted with a conjugate of cyclopentadiene and the peptide Gly-Arg-Gly-Asp-Ser-NH₂ (i.e. RGD-Cp) to install the peptide at the surface (Figure 1). This RGD peptide, found in the central cell-binding domain of fibronectin, mediates cell adhesion by binding to cellular integrin receptors.^[9] In previous work, we showed that monolayers presenting this peptide mixed with oligo(ethylene glycol) groups supported the integrin-mediated attachment and spreading of cells.^[10] Swiss 3T3 fibroblasts also attached and spread efficiently on dynamic substrates on which peptide was immobilized.^[11] Immunofluorescence microscopy showed that the adherent cells assembled focal adhesions and actin stress filaments (data not shown). Further, adherent cells could be released from the substrate when soluble Gly-Arg-

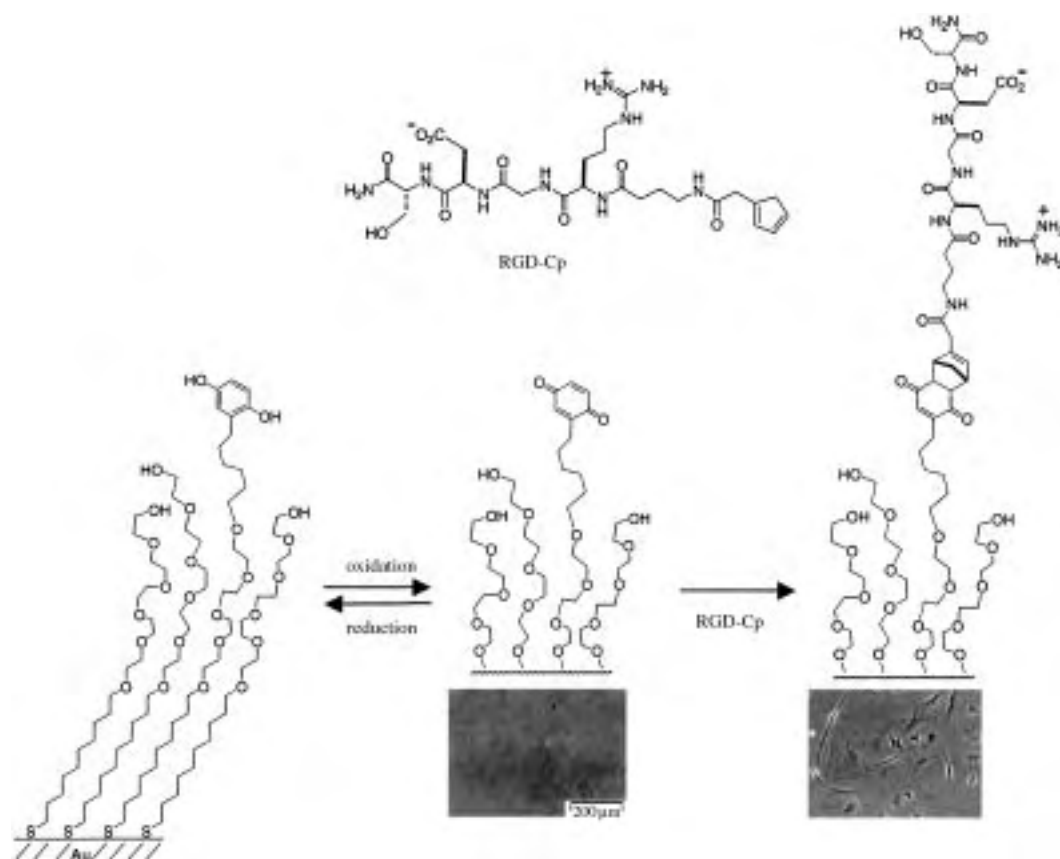


Figure 1. Strategy for the design of a substrate that can be electrically switched to turn on cell adhesion. A monolayer presenting a mixture of hydroquinone groups and penta(ethylene glycol) groups (left) is converted into a monolayer presenting the corresponding quinone groups (center) by application of a potential to the underlying gold. Both monolayers are inert to the attachment of cells (bottom left optical micrograph). Addition of a conjugate of cyclopentadiene and the peptide Gly-Arg-Gly-Asp-Ser-NH₂ to the monolayer presenting the quinone group results in the Diels–Alder-mediated immobilization of peptide (right). 3T3 Fibroblasts attach and spread on the resulting surface. Monolayers presenting the hydroquinone group are unaffected by the treatment with RGD-Cp and remain inert to cell attachment.

Gly-Asp-Ser-NH₂ (GRGDS) was added to the medium,^[10] confirming that adhesion to the monolayer was mediated entirely by the immobilized peptide ligands and that the surface was otherwise inert to nonspecific adsorption and matrix remodeling. We also found that monolayers presenting only penta(ethylene glycol) groups remained inert to cell attachment after an identical electrochemical and chemical treatment, showing that cell adhesion resulted from the Diels–Alder mediated immobilization of peptide.

We next demonstrate that the conditions required to turn on the immobilization of ligands are compatible with cell culture, and that this active substrate could turn on the migration and growth of cells *in situ*. We patterned a monolayer of hexadecanethiolate into circular regions (220 μ m in diameter) and derivatized the remaining bare regions of gold with a mixed monolayer presenting hydroquinone and penta(ethylene glycol) groups (Figure 2).^[12, 13] Immersion of the patterned substrate in a solution of fibronectin resulted in adsorption of protein only to the

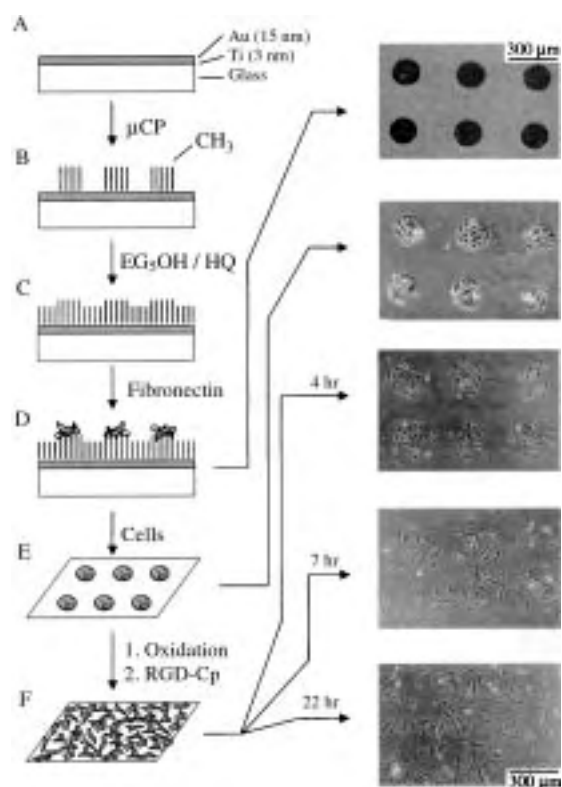


Figure 2. Example of turning on the migration and growth of cells with an electroactive substrate. A) Substrates were prepared by evaporating titanium (3 nm) and then gold (15 nm) onto glass coverslips. B) Micro-contact printing was used to pattern hexadecanethiolate into circles. C) A second monolayer was assembled on the remaining regions of gold by immersing the substrate into a solution of hydroquinone-terminated alkanethiol (HQ) and penta(ethylene glycol)-terminated alkanethiol (EG₅OH). D) The substrate was then immersed in a solution of fibronectin in PBS for four hours. A scanning electron micrograph shows that protein adsorbed only to the methyl-terminated regions of the monolayer. E) 3T3 Fibroblasts attached only to the circular regions presenting fibronectin, and when cultured in serum-containing media divided to fill these regions entirely. The surrounding inert monolayer strictly confined the cells to the circular regions. F) Electrochemical oxidation of the monolayer in the presence of serum-free media containing RGD-Cp (2 mM) led to the immobilization of the peptide and migration of cells from the circular regions.

circular regions. Swiss 3T3 fibroblasts attached only to these regions of the monolayer and proliferated to fill them completely. Cells remained confined to the circular regions for several days when cultured in serum-containing media. The inert regions of the substrate were turned on by applying an electrical potential of 500 mV (10 seconds) to the gold substrate in the presence of serum-free culture medium containing RGD-Cp (2 mM).^[14] The immobilization of RGD-Cp was essentially complete after two hours, at which time substrates were transferred to culture-media containing serum and maintained at 37 °C. Cells immediately began to migrate from the circular patterns onto the regions that were previously inert. After 7 hours most cells had moved completely off the pattern, and by 22 hours, the cells were evenly distributed on the substrate and the original pattern was no longer evident. After two days in culture, the cells had proliferated to give a near confluent layer across the entire substrate.^[15] Control experiments showed that oxidation of the substrate and addition of RGD-Cp were both required to induce cell migration from the patterned regions.

These substrates provide new opportunities for mechanistic studies of cell migration and for identifying molecules that affect migration in a novel screening assay. In the screening experiment, patterned cells are treated with candidate molecules at a specified concentration and for a designated period of time (Figure 3). The inert regions of the substrate

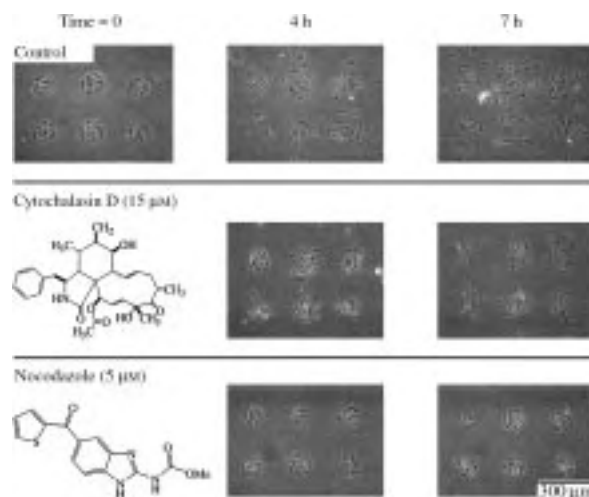


Figure 3. Example of a screening assay for compounds that influence cell migration. Top) 3T3 Fibroblasts patterned to a substrate. Upon electrochemical treatment and immobilization of RGD (described in Figure 2) the cells migrate to the pattern. Middle) Cells treated with Cytochalasin D migrate more slowly than cells on control substrates. Bottom) Cells treated with Nocodazole do not migrate from the pattern.

are then turned on by immobilization of RGD-Cp and cell migration is monitored. In three parallel experiments, cells were treated with either no compound, cytochalasin D, or nocodazole. Both compounds disrupt remodeling of the cytoskeleton and interfere with the migration process. Figure 3 shows the striking effects of the two drugs on migration. Nocodazole completely prevented migration of cells from the patterned regions, while cytochalasin D significantly retarded migration. When the medium was exchanged to remove the

compounds, cells resumed migration and proliferated to give a confluent layer, indicating the drugs were not cytotoxic over the time course of this assay.

This example establishes that the dynamic substrates are compatible with experiments to modulate cell behavior in situ and in real time. Our results suggest that this method will be broadly useful in assays for screening libraries of drug candidates that have antimigratory effects, and that can block metastasis in cancer.^[16] These substrates also offer immediate opportunities for mechanistic studies of cell migration including investigations of the dependence of cell migration on the density and affinity of immobilized ligands. Finally, these active surfaces can be combined with microelectrode arrays to modulate the presentation of ligands on select regions of the substrate and to even immobilize multiple ligands on the substrate.

The most important feature of this method is that these substrates are defined at the molecular scale and therefore provide complete control over ligand–receptor interactions between cell and substrate. The use of physical organic and synthetic chemistry was critical to the design and preparation of this dynamic substrate. This molecular approach is significant because it can be applied to the design of dynamic substrates having other functions, including those that selectively release immobilized ligands and that reversibly modulate the activities of ligands.^[17] Most importantly, the chemical approach described here provides unprecedented control in developing tailored substrates for modulating cell behavior, and will have an impact on programs in bioorganic chemistry, cell biology, and materials science.

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Asymmetric Induction by Helical Hydrocarbons: [6]- and [5]Helicenes**

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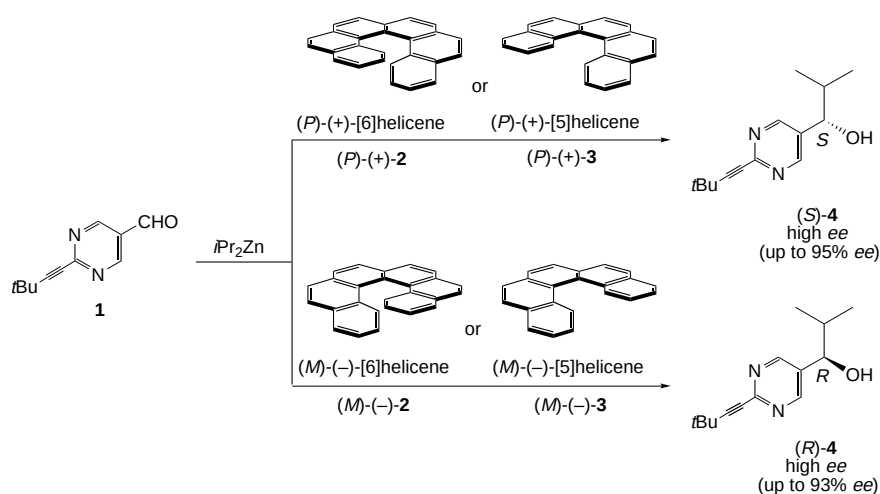
Enantiomerically enriched organic compounds that have been used as chiral catalysts and ligands in asymmetric synthesis possess a heteroatom(s) such as oxygen, nitrogen, sulfur, and phosphorus in addition to carbon and hydrogen atom(s).^[1] To the best of our knowledge, no chiral hydrocarbon has ever been used successfully as a chiral ligand or catalyst in asymmetric synthesis. On the other hand, [6]- and

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[5]helicene are hydrocarbons with chiral helical structures.^[2] However, helicene skeletons have rarely been used in enantioselective synthesis. Chiral phosphane ligands with helicene skeletons,^[3] and a chiral diol with a bis[5]helicene skeleton^[4] have been prepared and were used as a chiral ligand^[3a] and as a catalyst,^[4] respectively. In these cases, coordination of the phosphorus and oxygen atoms with metals is considered to play an essential role in the induction of asymmetry. It has thus been a challenge to induce asymmetry in enantioselective syntheses using helical hydrocarbons without any heteroatoms.

We report herein that chiral [6]- and [5]helicene act as chiral inducers in the highly enantioselective synthesis of a pyrimidyl alkanol by the enantioselective addition of diisopropylzinc ($i\text{Pr}_2\text{Zn}$) to 2-(2-*tert*-butylethynyl)pyrimidine-5-carbaldehyde (**1**; Scheme 1, Table 1). When aldehyde **1**



Scheme 1. Enantioselective synthesis of **4** in the presence of [6]- and [5]helicenes.

Table 1. Enantioselective synthesis of **4** in the presence of [6]- and [5]helicenes.

Entry	Helicene <i>ee</i> [%]	mol %	Method ^[a]	Alkanol 4 ^[b] Config. Yield [%] <i>ee</i> [%]
1	(<i>P</i>)-(+)- 2 >99.5	6.2	A	<i>S</i> 95 95
2	(<i>M</i>)-(-)- 2 >99.5	7.0	A	<i>R</i> 93 93
3	(<i>P</i>)-(+)- 3 67	11	A	<i>S</i> 88 95
4	(<i>M</i>)-(-)- 3 60	11	A	<i>R</i> 89 94
5	(<i>P</i>)-(+)- 2 ≈0.13	11	B	<i>S</i> 88 56
6	(<i>M</i>)-(-)- 2 ≈0.54	9.8	B	<i>R</i> 92 62

[a] Reactions were carried out in toluene at 0 °C. Method A: Aldehyde **1** and $i\text{Pr}_2\text{Zn}$ were added in two portions. Method B: Aldehyde **1** and $i\text{Pr}_2\text{Zn}$ were added in three portions. [b] The *ee* value was determined by HPLC analysis on a column fitted with a chiral stationary phase.

(0.05 mmol)^[5] was treated with $i\text{Pr}_2\text{Zn}$ (0.15 mmol)^[6] in the presence of (*P*)-(+)-[6]helicene ((*P*)-(+)-**2**; 6 mol %, >99.5% *ee*^[7]) at 0 °C in toluene, and aldehyde **1** and $i\text{Pr}_2\text{Zn}$ were successively added in two portions (0.2 and 0.8 mmol of aldehyde **1**, 0.48 and 1.92 mmol of $i\text{Pr}_2\text{Zn}$, respectively), (*S*)-5-pyrimidyl alkanol (*S*)-**4** was obtained (95% *ee*, 95% yield) (Table 1, entry 1). On the other hand, in the presence of (*M*)-(-)-**2** (7 mol %), the opposite enantiomer (*R*)-**4** was formed

(93% *ee*, 93% yield) (Table 1, entry 2). The sense of the asymmetric induction, in which [6]helicene (*P*)-(+)-**2** gives (*S*)-**4** and [6]helicene (*M*)-(-)-**2** gives (*R*)-**4**, is also the case with [5]helicene **3**.^[8] Thus, in the same way, the asymmetric addition of $i\text{Pr}_2\text{Zn}$ in the presence of (*P*)-(+)-**3** (11 mol %, 64% *ee*) gave (*S*)-**4** (95% *ee*, 88% yield) (Scheme 1; Table 1, entry 3), whereas in the presence of (*M*)-(-)-**3** (11 mol %, 60% *ee*), the reaction gave (*R*)-**4** (94% *ee*, 89% yield) (Table 1, entry 4). These high *ee* values and the absolute configurations of **4** may be rationalized as follows: 1) [6]- and [5]helicenes without any heteroatoms induce asymmetry in the initially formed zinc alkoxide of **4**, with the absolute configuration regulated by the *P* or *M* helicity of helicenes, and 2) asymmetric autocatalysis^[5, 9] of the zinc alkoxide of **4** with an amplification of *ee* affords alkanol **4** with very high *ee*.^[10, 11]

More significantly, (*P*)- and (*M*)-[6]helicenes with *ee* values as low as approximately 0.13% and 0.54% act as chiral inducers to afford (*S*)- and (*R*)-**4** with *ee* values of 56% and 62%, respectively (Table 1, entries 5 and 6). These moderate enantiomeric excesses can be considerably amplified by the consecutive asymmetric autocatalysis of **4**.^[9f]

[6]Helicene has been shown to form a diastereomeric charge-transfer complex with an enantiomer of a chiral aromatic compound with electron-withdrawing groups.^[12] In the present case, we postulate an interaction between [6]helicene and aldehyde **1** based on the calculated formaldehyde–benzene^[13] interactions and on the following ¹H NMR spectroscopy (300 MHz) results: the time-averaged chemical shifts measured from a solution of **1** in CDCl₃ (0.031M) shifted upfield upon the addition of [6]helicene. This shift showed an almost linear correlation with the addition of [6]helicene from 0 to 6.3 mol equivalents. Notably, the $\Delta\delta$ values of the signals for the aldehyde proton and for the protons of the pyrimidine ring are larger (–13.3 Hz and –9.1 Hz, respectively, per molar equivalent of [6]helicene)^[14] than those of the protons on the *tert*-butyl group (–1.1 Hz). This suggests a coordination of the [6]helicene with the carbonyl moiety and the pyrimidine ring of aldehyde **1**. When chiral [6]helicene coordinates with aldehyde **1**, it may differentiate between the *Re* and *Si* face of aldehyde **1**. When $i\text{Pr}_2\text{Zn}$ is added to aldehyde **1**, a nonracemic zinc alkoxide of alkanol **4** is considered to be formed initially.

In summary, we have described for the first time a highly enantioselective synthesis induced by chiral helical hydrocarbons. It should be emphasized that our present results formally correlate the chirality of circularly polarized light (CPL) and the chirality of an organic compound with high *ee* because [6]helicene is a well-accepted substrate that is enantioselectively (<2% *ee*) synthesized by CPL.^[11, 15]

Experimental Section

The alkylation in the presence of (P)-(+)-**2** with $\approx 0.13\%$ ee is representative (Table 1, entry 5). The ee value of **2** was determined by comparison of its specific rotation ($[\alpha]_D^{25} = +4.8^\circ$ ($c = 1.68$, CHCl_3)) with that of an enantiomerically pure sample (lit. [16] $[\alpha]_D^{20} = +3707^\circ$ ($c = 0.082$, CHCl_3)). A solution of $i\text{Pr}_2\text{Zn}$ in toluene (1M, 0.15 mL) was added dropwise over a period of 30 min at 0°C to a solution of aldehyde **1** (9.4 mg, 0.05 mmol) and (P)-(+)-**2** (36.9 mg, 0.11 mmol) in toluene (2.5 mL). After the mixture was stirred for 16 h, toluene (0.8 mL), a solution of $i\text{Pr}_2\text{Zn}$ in toluene (1M, 0.48 mL), and aldehyde **1** (37.6 mg, 0.2 mmol) in toluene (1.5 mL) were added successively. After 7 h, toluene (4.7 mL), a solution of $i\text{Pr}_2\text{Zn}$ in toluene (1M, 1.92 mL), and aldehyde **1** (151 mg, 0.8 mmol) in toluene (2 mL) were added, and the mixture was stirred for an additional 16 h. The reaction was quenched by the addition of hydrochloric acid (1M, 5 mL), and made alkaline by the addition of saturated aqueous sodium bicarbonate (15 mL). The mixture was filtered through celite, and the separated aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Purification of the residue by thin-layer chromatography on silica gel (developing solvent: hexane/ethyl acetate 2:1) gave pyrimidyl alkanol **4** (215 mg, 88%). The ee value was determined to be 56% by HPLC analysis using a chiral stationary phase (Daicel Chiralcel OD).

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Interprotein Electron Transfer Reaction Regulated by an Artificial Interface**

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Electron transfer (ET) reactions are fundamental to numerous important biological processes such as respiration, photosynthesis, and redox reactions of intermediary metabolism. In these systems, interprotein ET reactions are regulated by a specific interaction between two redox proteins. A unique charge distribution on the protein surface is responsible for this recognition. For example, cytochrome *c*, an electron carrier between complexes III and IV of the respiratory chain, has several highly conserved lysine residues surrounding the slightly exposed heme edge, while redox partners have a recognition domain consisting of anionic residues with the same topological symmetry as the lysine

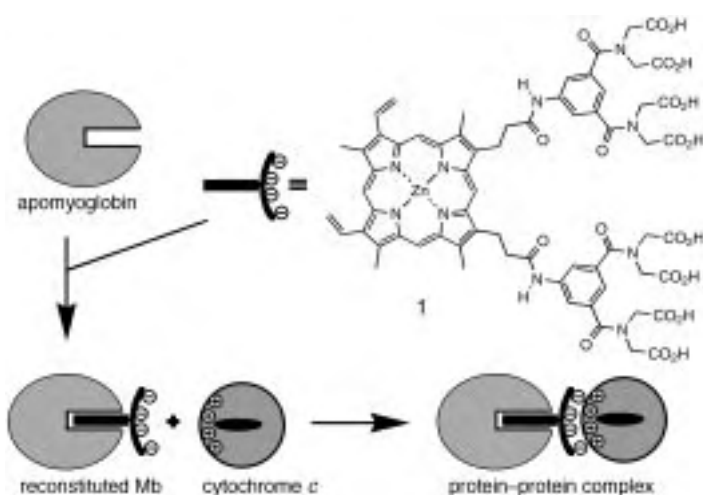
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residues of cytochrome *c*. A series of studies utilizing mutagenesis, kinetics, X-ray crystal-structure analysis, and computational docking show that the electrostatic interaction between charged patches on each protein surface guides them to an optimal orientation of the reactant complex for facile ET.^[1–4] Over the last decade, a large number of synthetic models have been developed to elucidate the factors that determine the biological ET reaction rate; however, ET model studies on the interfacial recognition of interprotein ET reactions are largely unknown.^[5–7]

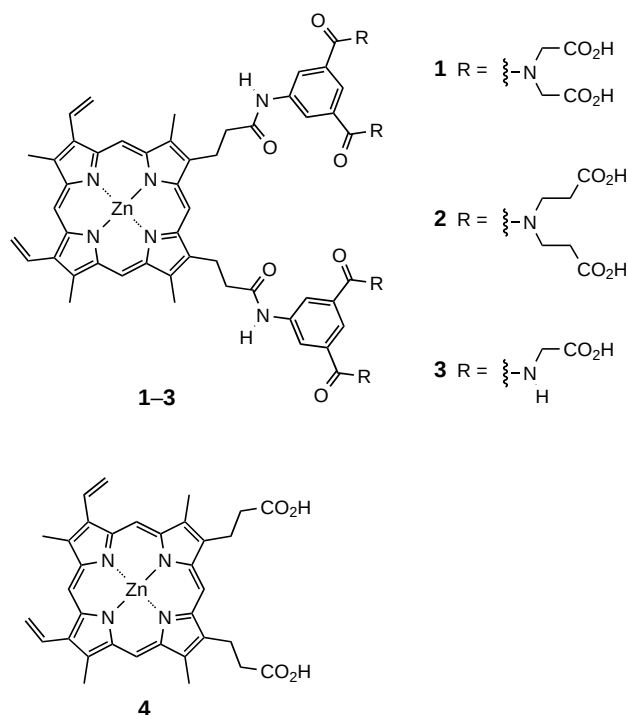
Herein we report on an interprotein ET reaction regulated by artificial recognition interfaces between cytochrome *c* and a series of reconstituted myoglobins (rMbs). Recently, we reported on rMb(1), having a functionalized zinc porphyrin **1** as a prosthetic group, which can form a protein–protein complex with cytochrome *c* through electrostatic interactions as shown in Scheme 1.^[7] The cytochrome *c* recognition unit



Scheme 1. Preparation of a reconstituted myoglobin bearing a cytochrome *c* receptor and the formation of a protein–protein complex with cytochrome *c*.

introduced on the myoglobin (Mb) surface has a total of eight carboxylates around two rigid and hydrophobic benzene rings at the terminal of the heme propionates. On this surface the negative charges should spread over approximately $15 \text{ \AA}^2$ to match the situation in the lysine residues in the binding domain of cytochrome *c*. We found that rMb(1) works as an artificial ET protein, which efficiently photochemically reduces cytochrome *c* by forming the stable protein–protein complex. The facile construction of various recognition interfaces on the protein surface might provide a novel ET model which can be used to systematically understand the role of recognition interfaces in interprotein ET reaction.

Based on rMb(1), we designed the zinc myoglobins rMb(2) and rMb(3) which are a new type of cytochrome *c* receptor. Zinc porphyrins **1** and **2**, with the same number of carboxylates, differ in the flexibility of the attached receptor units. Zinc porphyrin **3** has four carboxylates, which provide a control for probing the charge number required for cytochrome *c* recognition. Zinc porphyrins **1–3** were synthesized according to the reported procedure, and then incorporated



into apoMb.^[7] The resultant species rMb(1)–rMb(3) were purified on cation-exchange and gel columns. Similarly, a native zinc myoglobin, rMb(4) with the protoporphyrin zinc complex **4** was prepared as a reference protein. The UV/Vis spectra of rMb(1)–rMb(3) are virtually identical to that of rMb(4) (see Experimental Section).

Binding features and interprotein ET between cytochrome *c* and rMb(1)–rMb(4) were investigated using flash photolysis analysis. The excitation by laser of the porphyrin π system produces a triplet excited state of rMb(1)–rMb(4), $^3\text{rMb(1)}\text{--}^3\text{rMb(4)}$, with intersystem crossing. The natural decay of $^3\text{rMb(1)}\text{--}^3\text{rMb(4)}$, a return to the ground state, was studied by monitoring the absorbance at 460 nm which corresponds to the transient absorbance difference between ^3rMb and rMb (Figure 1a). In the absence of cytochrome *c*, the decay profiles of $^3\text{rMb(1)}\text{--}^3\text{rMb(3)}$, have single exponen-

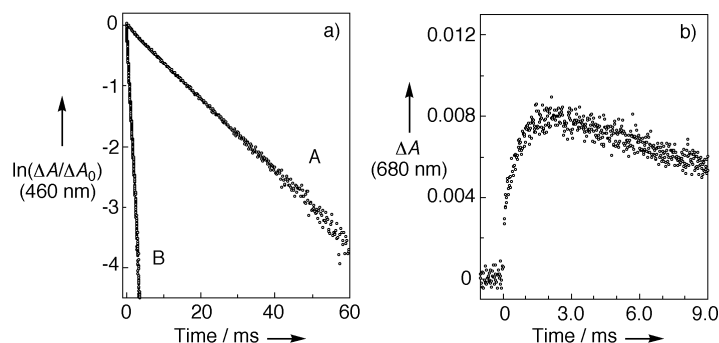


Figure 1. a) Triplet decay traces for rMb(2) in the absence (trace A) and presence (trace B) of cytochrome *c*. b) Transient absorption for the ET intermediate of rMb(2) under the same conditions as for trace B. Conditions: Phosphate buffer ($\mu = 10 \text{ mM}$, pH 7.0), 293 K; $[\text{rMb(2)}] = 3.8 \times 10^{-6} \text{ M}$; $[\text{cytochrome c}] = 1.0 \times 10^{-6} \text{ M}$.

tial functions with $k_D = 59 \pm 1 \text{ s}^{-1}$, which is identical to the value observed for $^3\text{rMb(4)}$. Adding cytochrome $c(\text{III})$ to solutions containing rMb resulted in a dramatic acceleration of the decay rate of ^3rMb with a single exponential remained. In contrast to that, no acceleration was observed upon addition of cytochrome $c(\text{II})$, which indicates that the quenching is the result of an ET reaction from rMb to cytochrome $c(\text{III})$. Furthermore, the appearance and disappearance of ET intermediates as well as of the zinc porphyrin cation radical of rMb and cytochrome $c(\text{II})$, were observed at 680 nm (Figure 1b) and 550 nm, respectively. The observed decay rate constants (k_{obs}) of $^3\text{rMb(1)} - ^3\text{rMb(4)}$ are plotted for the concentration of cytochrome $c(\text{III})$ in Figure 2. The quenching

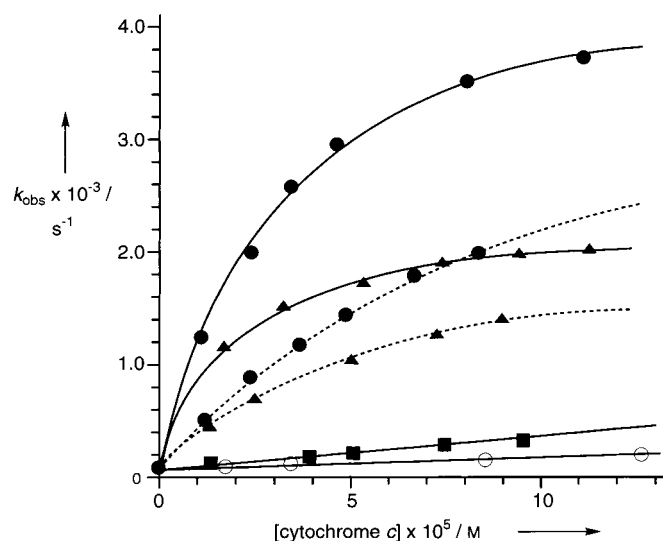


Figure 2. Decay rate of the triplet state of rMb(1)–rMb(4) as a function of cytochrome c concentration, in phosphate buffer at pH 7.0 and 293 K. $\blacktriangle$ = rMb(1); $\bullet$ = rMb(2); $\blacksquare$ = rMb(3); $\circ$ = rMb(4). The initial concentration of rMb is $4.3 \times 10^{-6} \text{ M}$, the lines are fitting curves and the ionic strengths are 10 mM (solid line) and 20 mM (dashed line).

of $^3\text{rMb(3)}$ and $^3\text{rMb(4)}$ is enhanced linearly with the concentration of cytochrome $c(\text{III})$. This linearity is consistent with the simple collisional quenching mechanism, which does not necessarily require the existence of a stable protein–protein complex. In this case, the triplet quenching rate (k_q) is given by [Eq (1)], where C represents the concentration

$$k_{\text{obs}} = k_D + k_q C \quad (1)$$

of cytochrome $c(\text{III})$. From the fitting of the slope by [Eq (1)], the values of k_q are determined to be $(2.2 \pm 0.2) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ and $(8.0 \pm 0.3) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for rMb(3) and rMb(4), respectively.^[8] The k_q of rMb(3) is 2.8-fold faster than that observed for native rMb(4), which clearly indicates that the artificially introduced anionic recognition unit can serve as an attractive interaction site for cytochrome c . However, the charge introduced to rMb(3) is not enough to make a stable complex with cytochrome c through electrostatic interactions. On the other hand, $^3\text{rMb(1)}$ and $^3\text{rMb(2)}$ were very efficiently quenched by cytochrome $c(\text{III})$. The quenching rates increase

nonlinearly with the concentration of cytochrome $c(\text{III})$ and level off at higher concentrations. This saturation can be accounted for by a quenching mechanism involving a fast equilibrium between the complex and its components. The electron transfer rate within the intracomplex ET (k_{intra}) and binding affinity (K_a) between cytochrome c and rMb are given by [Eq (2)], where f and M represent the fraction of

$$k_{\text{obs}} = k_D + k_{\text{intra}} f \\ = k_D + k_{\text{intra}} [M + C + 1/K_a - \{(M + C + 1/K_a)^2 - 4MC\}^{1/2}] / 2M \quad (2)$$

complexed rMb and the total concentration of rMb, respectively. The experimental data at 10 and 20 mM ionic strength were fitted to [Eq (2)] by an iterative, nonlinear least-squares routine to yield a rate constant for intracomplex ET and binding affinities between cytochrome $c(\text{III})$ and rMb(1), and between cytochrome $c(\text{III})$ and rMb(2). The values of K_a and k_{intra} are summarized in Table 1. The binding affinities of

Table 1. The ET rate constants and binding constants between rMb and cytochrome c .^[a]

	Ionic strength	$k_{\text{intra}} \times 10^{-3} [\text{s}^{-1}]$	$K_a \times 10^{-4} [\text{M}^{-1}]$
rMb(1)	$\mu = 10 \text{ mM}$	2.2 ± 0.1	6.5 ± 0.3
	$\mu = 20 \text{ mM}$	2.2 ± 0.1	1.5 ± 0.6
rMb(2)	$\mu = 10 \text{ mM}$	4.8 ± 0.2	3.1 ± 0.2
	$\mu = 20 \text{ mM}$	4.8 ± 0.2	0.83 ± 0.1

[a] All data were obtained at 293 K in phosphate buffer, pH 7.0.

rMb(2) are 2.1- and 1.8-fold smaller than those of rMb(1) at 10 mM and 20 mM ionic strength, respectively. This difference in the affinities for cytochrome c ($\Delta\Delta G = 1.8$ and $1.4 \text{ kcal mol}^{-1}$ at 10 and 20 mM ionic strength, respectively) arises from the difference in flexibility of recognition interfaces between rMb(1) and rMb(2). In contrast, k_{intra} was greater for rMb(2) than for rMb(1).

Previous NMR spectroscopic studies revealed that the rMb recognizes the same region of cytochrome c that its physiological partners do.^[7, 9] In the docking complex of the rMb and cytochrome c , therefore, the heme of cytochrome c is expected to be in the vicinity of the recognition units. This expectation is also supported by a small difference between the binding constants observed for rMb(1) and rMb(2). Accordingly the ET rates should not be greatly altered, even though the additional methylene groups of **2** could slightly decrease the electron coupling and the ET rate. However, k_{intra} for rMb(2) is 2.2-fold larger than that observed for rMb(1). This result may be because the interface of the rMb(2)–cytochrome c complex is more flexible than that of rMb(1). This difference cannot be explained simply from the static structural viewpoint.

Recent discussion on ET reactions has pointed out that the observed ET rate is not a real ET rate constant when the redox reaction is controlled by a non-ET process.^[10c, 11] If a protein–protein complex is undergoing interconversion between several conformational forms, then this process influences the observed ET rate constant. In fact, a protein–protein complex often adopts multiple conformational states. In some cases it has been reported that an interprotein ET reaction is

regulated by configurational rearrangement in the complex.^[10, 12, 13] These considerations lead us to one possible interpretation for the observed data: the rMb–cytochrome *c* complex exists in several conformational states. The most stable conformation, which contributes the most to the apparent binding constant, is not the most reactive conformation. The interfacial dynamics within the complex induce the most reactive conformation for ET, for example, with the heme of cytochrome *c* and the recognition units in contact. The more flexible recognition interface in the rMb(2)–cytochrome *c* complex facilitates this rearrangement. As a consequence, an apparent ET rate in the rMb(2)–cytochrome *c* system is faster than that of the rMb(1)–cytochrome *c* complex. At the moment, however, we do not exclude other possibilities. Further work will be done to reveal the detail mechanism of the ET reaction.

In summary, we have designed and constructed a novel *synthetic model* of interprotein ET to evaluate the importance of protein–protein recognition at a molecular level. Binding properties and overall ET rates observed for rMb(1) and rMb(2) clearly demonstrate the importance of the interfacial dynamic feature of the interprotein ET reaction. Although recently temperature and viscosity dependence of interprotein ET revealed that the ET reaction can be regulated by configurational changes,^[12, 13] to our knowledge this is the first study that directly shows the control of the interprotein ET reaction by the flexibility of the recognition interface. Moreover, the data presented here show that a strict recognition does not necessarily result in efficient ET, although a proper recognition domain is required for an interprotein ET reaction.

Experimental Section

Preparation of reconstituted myoglobins. ApoMb was prepared from horse heart metMb (Sigma) by Teale's 2-butanone method.^[14] The solution of apoMb (0.4 mM) was mixed with **2** or **3** (1.0 equiv) and allowed to stand over 12 h at 4 °C. The mixture was passed through Sephadex G-25 and CM-cellulose columns; rMb(1): UV/Vis (phosphate buffer, pH 7.0) (λ_{max} [nm] (relative intensity)): 428 nm (1.0), 555 (0.065), 595 (0.051); rMb(2): UV/Vis (phosphate buffer, pH 7.0) (λ_{max} [nm] (relative intensity)): 428 (1.0), 555 (0.056), 595 (0.044); rMb(3): UV/Vis (phosphate buffer, pH 7.0) (λ_{max} [nm] (relative intensity)): 428 (1.0), 555 (0.061), 595 (0.051); rMb(4): UV/Vis (phosphate buffer, pH 7.0) (λ_{max} [nm] (relative intensity)): 428 (1.0), 555 (0.065), 595 (0.051). Further preparative and analytical data can be found in the Supporting Information.

Laser flash photolysis studies: the nanosecond laser photolysis studies were carried out with a Q-switched Nd:YAG laser, which delivered 6-ns pulses at 532 nm. The incident energy was about 10 mJ. The probe source was a continuous 150-W xenon arc lamp passed through a monochromator. Signals were detected in transmission using a photo multiplier (Hamamatsu Photonics, R2949) and the transient signals were digitized using Tektronix TDS 320 oscilloscope. Signals were averaged 1000 to 5120 times. The data were transferred to a NEC PC9821Ae computer for further data analysis. No smoothing artifact affected the results of the data analysis. The sample solution containing Mb and cytochrome *c* (horse heart, Sigma) in a 10-mm quartz cell was prepared in a glove box. The rMb concentration was about $3.8\text{--}4.3 \times 10^{-6}$ M. The temperature was maintained at 293 K using a NESLAB circulation system.

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Three-Dimensional Transmission Electron Microscopic Observations of Mesopores in Dealuminated Zeolite Y**

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Zeolites are microporous crystalline aluminosilicates, which makes them very suitable for separation processes or shape-selective catalysis. The micropores of zeolites often induce advantageous shape selectivity, but enhanced accessibility is frequently desirable to restrict mass-transfer effects and/or allow catalytic conversion of larger molecules. Several approaches have been followed to enhance accessibility,^[1] such as the development of zeolites with intrinsically larger pores,^[2] delaminated zeolite precursors,^[3] and zeolite nanocrystals.^[4] A widely applied method to enhance accessibility is the creation of materials with both micropores (<2 nm diameter) and mesopores (2–50 nm diameter). This can be done by special synthetic techniques^[5] or by postsynthetic modification of zeolites with hydrothermal treatment (steaming) or acid leaching.^[6] Steaming and acid-leaching treatments generate mesopores by extracting aluminum from the zeolite lattice, thus causing a partial collapse of the framework. Up to now, the characterization of these mesopores has been done with nitrogen physisorption and transmission electron microscopy (TEM).^[7] However, the visualization of the mesopores with conventional TEM gives no information about the shape, connectivity, and three-dimensional orientation of the pores. Furthermore, the zeolite crystals are often cut into thin slices with an ultramicrotome to investigate the pores. This may fracture the zeolite crystal, which hinders the interpretation of the TEM images. Recently, the mesoporous structure of MCM-48 has been determined by electron crystallography.^[8] However, this method is suitable only for materials with well ordered pores. With three-dimensional transmission electron microscopy (3D-TEM) it is possible to image (random) mesopores of an intact zeolite crystal in three dimensions.^[9] Herein, we show 3D-TEM results of the size, shape, and connectivity of the mesopores in a series of (steamed/acid-leached) Y zeolites. Moreover, a quantitative comparison between the 3D-TEM images and nitrogen physisorption is made. This enables us to propose a detailed model for the generation of mesopores.

3D-TEM, sometimes referred to as electron tomography,^[10] is a technique in which a series of 2D TEM images (scattering contrast) is recorded, that is subsequently used to compute a 3D image (3D reconstruction) of the investigated object.^[9–12] By virtual cross-sectioning of such a 3D reconstruction, one can reveal the interior of the object. To study the generation of mesopores, we used a series of Y zeolites with increasing mesopore volume, namely, NaY, USY (Ultra Stable Y), and XVUSY (eXtra Very Ultra Stable Y). The USY sample is a steamed NH₄Y, whereas the XVUSY is steamed twice and extensively acid leached. The physical properties of these samples are given in Table 1.

Table 1. Physical properties of NaY (CBV100), USY (CBV400) and XVUSY (CBV780)

	Si/Al bulk [at/at]	Si/Al XPS [at/at]	<i>a</i> ₀ [nm]	% Y ^[a]	<i>V</i> _{micro} ^[b] [mL g ^{−1}]	<i>V</i> _{micro} ^[c] [mL g ^{−1}]	<i>V</i> _{meso} ^[d] [mL g ^{−1}]	<i>S</i> _T ^[e] [m ² g ^{−1}]
NaY	2.6	2.8	2.469	100	0.341	0.341	0.053	8
USY	2.6	1.1	2.450	87	0.256	0.324	0.108	63
XVUSY	39.3	71.3	2.423	72	0.277	0.267	0.251	120

[a] Relative crystallinity. [b] Micropore volume from *t*-plot; *t* = [14.3600/(0.1013 − lg(*P*/*P*₀))] ^{0.5}. [c] Expected micropore volume if all micropores are empty; calculated by correcting *V*_{micro} of NaY for crystallinity, *a*₀, and sodium mass of USY and XVUSY. [d] *V*_{total} − *V*_{micro}. [e] Sum of external and mesopore surface area calculated from *t*-plot.^[13]

In Figures 1–3, 2D-TEM images and thin slices through the 3D-TEM reconstructions are shown for NaY, USY, and XVUSY, respectively (all scale bars represent 200 nm). In the

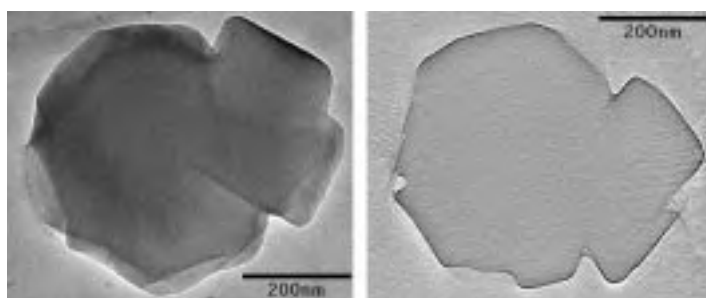


Figure 1. a) 2D-TEM image of a NaY crystal taken at a magnification of ×15k and b) a thin (1.7 nm) slice through the 3D-TEM reconstruction of this crystal.

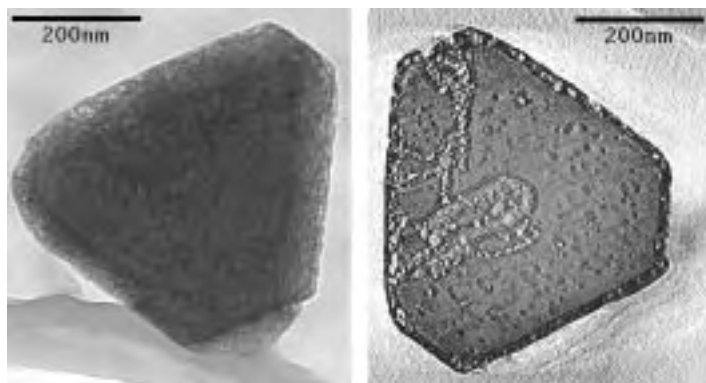


Figure 2. a) 2D-TEM image of a USY crystal taken at a magnification of ×15k and b) a thin (1.7 nm) slice through the 3D-TEM reconstruction of this crystal.

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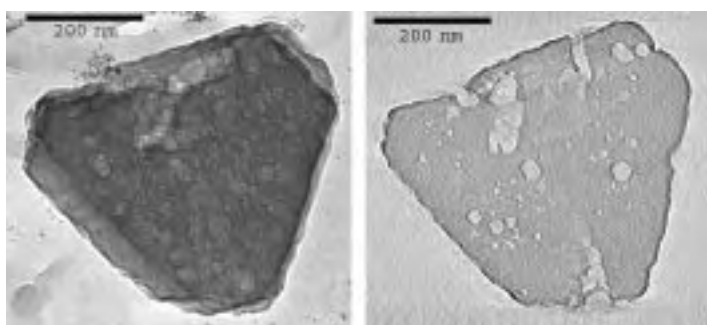


Figure 3. a) 2D-TEM image of an XVUSY crystal taken at a magnification of $\times 20k$ and b) a thin (1.25 nm) slice through the 3D-TEM reconstruction of this crystal. Small gold particles (5 nm), used as markers, are observed in Figure 3a.

conventional TEM images, the mesopores of USY and XVUSY are just visible as lighter areas, whereas, in the thin slices through the 3D-TEM reconstructions of USY and XVUSY, the mesopores can be distinguished very well as light areas. In line with the physisorption results (Table 1), NaY does not show any mesopores in both the 2D- and 3D-TEM images; the same holds for NH_4Y (not shown). This indicates that the light areas in Figure 2b and 3b really are the mesopores and not an artifact of the reconstruction. The diameters of the mesopores visualized with 3D-TEM are 3–20 nm for USY and 4–34 nm for XVUSY. This is in excellent agreement with the pore-size distributions calculated from the nitrogen desorption isotherms: 4–20 nm and 4–40 nm for USY and XVUSY, respectively. The large porous area in the USY crystal (Figure 2b, center left) is not a single pore but consists of many small cavities separated by thin walls. This explains why no pores larger than 20 nm are found from the nitrogen adsorption–desorption experiments. The 3D-TEM reconstructions also show that in USY and XVUSY the majority of the mesopores are cavities, although there are also some cylindrical pores connecting the outer surface with the interior of the zeolite crystallite. The shape of the hysteresis loop in the nitrogen physisorption isotherms of USY and XVUSY is indicative for inkbottle-type pores combined with cylindrical pores. The cavities visualized with 3D-TEM are most likely connected to the microporous system of the zeolite, thus giving inkbottle type adsorption–desorption behavior in physisorption.

In the cross-section of the 3D-TEM reconstruction of the USY crystal (Figure 2b), some dark cavities (5–20 nm diameter) and a dark band (about 15 nm thick) on the outer surface are also visible. TEM studies have shown that the dark areas inside and outside the crystals of steamed zeolites are most likely amorphous alumina deposited in the mesopores and on the external surface during the steaming process.^[7a–c, 14] Therefore, we believe that the dark areas in our 3D-TEM reconstruction are not artifacts of the reconstruction but the imaging of confined material in the mesopores and amorphous alumina deposited on the external surface. In the XVUSY sample, no confined material could be detected (Figure 3b) because this has been removed during the severe acid-leaching step. When the bulk Si/Al ratio is compared with the surface Si/Al ratio obtained with XPS (Table 1), it is

clear that only for USY is there an enrichment of the external surface of the crystals with aluminum. This supports our 3D-TEM observations that only for USY there is a dark band of amorphous alumina on the external surface.

From the 3D-TEM observations, we propose a detailed model for the generation of mesopores in dealuminated zeolite Y (see Figure 4). The model largely supports earlier

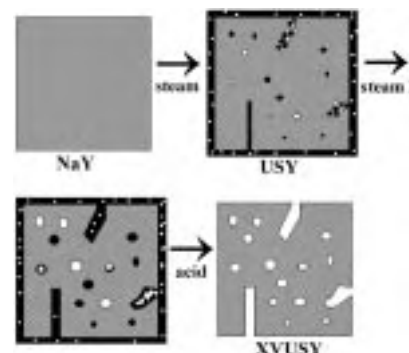


Figure 4. Model for the generation of mesopores in zeolite Y. The zeolite is gray, the amorphous alumina is black, and the empty mesopores are white.

ones^[7a–c, 15] but adds key aspects of mesopore generation. During the steaming process (from NH_4Y to USY), aluminum ions are extracted from the zeolite lattice and deposited in the micro- and mesopores and on the external surface of the crystals.^[16] This is confirmed by the decrease of the zeolite unit cell, the dark areas in the cross-sections of the 3D-TEM reconstruction of USY, and the surface enrichment with aluminum of the USY sample as observed with XPS (Table 1). The measured micropore volume for USY is lower than the value expected if all micropores were empty (Table 1; V_{micro} versus $V_{\text{micro}}^{\text{calcd}}$), which indicates that confined material is also present in the micropores. During the extraction of aluminum from the lattice, mobile silicon species from defect sites (where aluminum has been extracted) cause some defect sites to develop into cavities in the zeolite crystals and other defect sites to vanish by healing the framework. The volume and shape of the mesopores, determined by nitrogen physisorption and 3D-TEM, confirm this cavity-formation mechanism. Thus, the mesoporous system is primarily formed through cavities inside the crystals and not through pores connecting the interior of the crystals with the external surface. During the second steaming step in the generation of XVUSY, small cavities close to one another (as visible in Figure 2b) form larger cavities and cylindrical pores, which can be seen from the nitrogen physisorption measurements and 3D-TEM reconstructions. By acid leaching of the steamed sample, extra-framework aluminum species in the micro- and mesopores and on the external surface area dissolve.^[6, 14] This is confirmed by the 3D-TEM reconstruction of XVUSY, which shows neither any confined material in the mesopores nor amorphous alumina on the external surface. Furthermore, XPS shows no surface enrichment in aluminum for XVUSY and the measured and “expected” micropore volume (Table 1) are comparable. Despite the development of a mesopore system, 2D- and 3D-TEM images show that the crystals

remain intact during the steaming and acid-leaching steps. Furthermore, the pore-size distribution from the nitrogen-desorption isotherm of all three samples shows an additional peak at a pore diameter of 70 nm. That this peak, which is caused by the interstitial space between the crystals, is at the same position for all three samples indicates that the crystals of these samples are of the same order of magnitude. This is different from the results obtained by Beyerlein et al.,^[7a-c] who claimed extensive fracturing of zeolite Y crystals.

Thus, the pores in a series of dealuminated zeolite Y have been imaged in order to gain insight in the shape and three-dimensional ordering of the mesopores in the zeolite crystallites. Based on the surprising result, that most of the mesopores are present as cavities rather than cylindrical pores connecting the external surface with the interior of the crystallite, a more detailed model for the generation of these mesopores is proposed. However, the shape of the mesopores also raises the question to what extent the accessibility and diffusion are enhanced by the formation of these cavities.

Experimental Section

Samples CBV100 (NaY), CBV400 (USY), and CBV780 (XVUSY) were obtained from Shell International Chemicals and Zeolyst. Nitrogen adsorption and desorption measurements (Micromeritics ASAP 2010) were performed at liquid nitrogen temperature. XPS measurements (Vacuum Generators XPS) were performed on a system using nonmonochromatic Al_{Kα} radiation at an anode current of 20 mA at 10 keV. For electron microscopy, a droplet of a colloidal gold suspension (Sigma, 5 nm gold) was dried on a carbon-coated copper grid, thus providing markers for the alignment of the data set. Next, a droplet of a suspension of the sample in ethanol was dried on this grid. From a representative crystal, a tilt series of about 141 images was taken from about +70° to -70° at 1° intervals of magnification ×15 k or ×20 k on one of two microscopes (Philips CM 200 FEG or a Tecnai 20) at 200 kV and with software for automated electron tomography.^[12] From the tilt series, a 3D-reconstruction of the crystal is calculated as a stack of thin (1–2 nm) slices.^[9–12]

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Fluorescence Detection of Specific RNA Sequences Using 2'-Pyrene-Modified Oligoribonucleotides**

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Fluorescence detection of specific RNA sequences is an area of much current interest and activity. It is important for the investigation of the regulatory mechanisms of gene expression^[1, 2] and diagnostic analysis of infectious organisms from viruses or bacteria.^[3, 4] Recent works have focused on the design and synthesis of fluorescent oligonucleotides that exhibit an enhanced signal upon hybrid formation,^[5–14] since these type of probes can be used in homogeneous, as well as heterogeneous, assays. The enhanced fluorescence has facilitated monitoring in vitro transcription,^[15] ribozyme reaction,^[16, 17] and RNA folding.^[18]

Our research efforts have concentrated on the use of the sugar 2'-position as the site in the covalent attachment of several fluorophores.^[19–22] In particular, the incorporation of pyrene, via a one carbon-atom linker, into the specified position of oligodeoxyribonucleotides has provided a probe that exhibits strong fluorescence upon binding to RNA.^[21, 22] While the potential of these probes is appreciated, it has remained unfulfilled because the pyrene–DNA complexes are plagued by the sequence limitation of the probe or the positioning of C or G bases at the 3'-site of the pyrene modification to gain a measurably strong fluorescence.^[22] We now disclose a new pyrene probe derived from RNA that overcomes this limitation. The pyrene fluorescence is signifi-

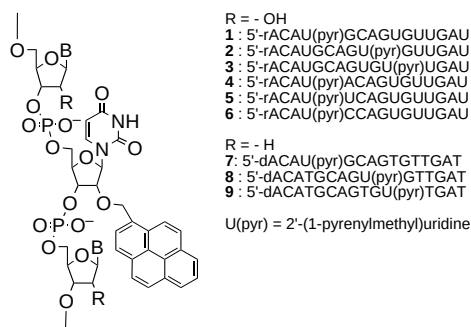
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cantly enhanced upon hybridization to RNA, which is not dependent on the choice of probe sequence, but very sensitive to a mismatched base present in the target RNA. This is the first example of RNA base-mismatch recognition by pyrene fluorescence.^[23]

We prepared RNA oligonucleotides possessing a pyrenylmethyl group at several different sugar residues and pyrene-modified DNA oligomers of the same sequences for comparison (Scheme 1). Binding properties for both the pyrene-



Scheme 1. RNA oligonucleotides with a pyrenylmethyl group located on various sugar residues.

modified RNA and DNA are shown in Table 1. The melting temperatures T_m of all the pyrene-modified duplexes differed slightly, by 0 to 5 °C, from those of the corresponding unmodified duplexes.

Table 1. Melting temperatures (260 nm) and fluorescence quantum yields of pyrene-modified oligonucleotide duplexes.

Oligomer	T_m ^[a] [°C]		Fluorescent Φ		
	duplex with DNA	duplex with RNA	single-stranded oligomer	duplex with DNA	duplex with RNA
RNA 1 ^[b]	47.1	56.5			
1	50.0	53.3	0.005	0.007	0.098
2	48.6	52.9	0.007	0.004	0.113
3	46.9	52.4	0.006	0.004	0.119
RNA 2 ^[c]		53.9			
4		50.6	0.008		0.102
RNA 3 ^[d]		52.1			
5		49.5	0.007		0.162
RNA 4 ^[e]		58.9			
6		54.0	0.007		0.237
DNA 1 ^[f]	53.9	49.1			
7	53.6	46.9	0.006	0.005	0.006
8	50.5	45.3	0.004	0.006	0.007
9	48.2	44.2	0.005	0.007	0.006

[a] Monitored at 260 nm. [b] RNA 1 = 5'-rACAUACAGUGUUGAU. [c] RNA 2 = 5'-rACAUACAGUGUUGAU. [d] RNA 3 = 5'-rACAUACAGUGUUGAU. [e] RNA 4 = 5'-rACAUACAGUGUUGAU. [f] DNA 1 = 5'-dACATGCAGTGTGAT.

Table 1 summarizes the fluorescent quantum yields Φ of the pyrene-modified RNA and DNA before and after hybridization. The fluorescence spectra for RNA **2** and DNA **8** are shown as examples in Figure 1. The single-stranded probes exhibit typical pyrene-monomer emission, whose quantum efficiencies were very low. Upon binding with RNA, the fluorescence of the pyrene-RNA complex was significantly

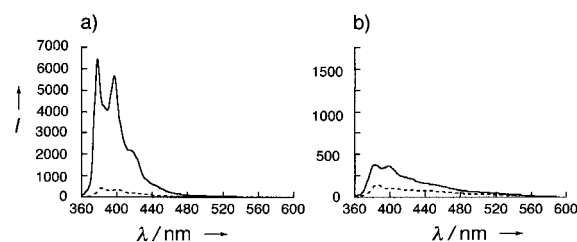


Figure 1. Fluorescence spectra of a) pyrene-modified RNA **2** (---) and its duplex with RNA (—) and b) pyrene-modified DNA **8** (---) and its duplexes with RNA (—).

enhanced, whereas the fluorescence enhancement of the pyrene-DNA complex was not high. All the pyrene-modified RNA/RNA duplexes displayed strong emissions, whose Φ values ranged from 0.1 to 0.23. These values are comparable to those for 1-pyrenebutyric acid ($\Phi = 0.30$) and 1-pyrenylmethanol ($\Phi = 0.25$) in an air-saturated aqueous solution. The extent of the fluorescence enhancement upon hybridization was not highly dependent on the probe sequence around the pyrene modification. This is in contrast to previous observations for pyrene-modified DNA.^[21] Upon binding to DNA, the fluorescence of both the pyrene-RNA and -DNA complexes were not largely altered.

It is well documented that the nucleobases serve as an efficient quencher for pyrene fluorescence.^[24–28] Fluorescence quenching of pyrene occurs in both noncovalent and covalent complexes of nucleosides and single-stranded oligonucleotides.^[29–31] In a similar manner, introduction of the pyrene into the 2'-position of oligonucleotides resulted in strong fluorescence quenching. The quenched emission recovers in pyrene-modified RNA/RNA duplexes to a level that is as strong as the free pyrene compounds in an aqueous solution. The pyrene located outside of the RNA/RNA duplex is likely to be responsible for the strong emission, which was supported by the fluorescence excitation and CD studies.^[22]

The fluorescence and melting data for hybrids of the pyrene-modified RNA with RNA possessing a single base

Table 2. Relative fluorescence intensity and T_m values for the duplexes of pyrene-modified RNA oligonucleotide **1** or **6** with RNA containing a single base mismatch.

pyrene-modified RNA	RNA ^[a]	Relative fluorescence intensity ^[b]	T_m [°C]
1	5'-rAUCAACACUGCAUGU	16	53.3
	5'-rAUCAACACUG C UGU	1	45.2
	5'-rAUCAACACUG C CUGU	1	46.8
	5'-rAUCAACACUG C UUGU	1	44.7
	5'-rAUCAACACUG G AUGU	1	46.7
	5'-rAUCAACACUG A AUGU	1	44.7
6	5'-rAUCAACACUG U AUGU	4	50.5
	5'-rAUCAACACUG G AUGU	59	54.0
	5'-rAUCAACACU U AUGU	2	44.1
	5'-rAUCAACAC G GGAUGU	52	43.3
	5'-rAUCAAC G CUGGAUGU	56	48.3
	5'-rAUCA C ACUGGAUGU	54	44.5
	5'-rAUC U ACUGGAUGU	56	44.1

[a] The mismatch bases in RNA sequences are indicated by the bold font.

[b] Relative fluorescence intensities at 380 nm were obtained at 23 °C based on the single-stranded pyrene-modified oligonucleotide **1** or **6**.

mismatch are shown in Table 2. Little or no fluorescence changes were observed in binding of the pyrene probe to RNA possessing a mismatch facing the modified nucleoside. Similarly, the mismatch at the 5'-site near the pyrene modification in the target RNA affected the duplex fluorescence. In contrast, an RNA mismatch at the site separated more than three bases from the pyrene did not show significant effect on the duplex fluorescence. These observations strongly suggest that the base pairings at the neighboring positions of the modification are important for rearrangements of the local structural elements to yield a strongly emitting pyrene moiety in the duplex.

The structural basis for the different fluorescence properties between pyrene-modified RNA/RNA and pyrene-modified DNA/DNA duplexes requires further investigation. With high quantum efficiency, sequence specificity, and binding affinity, RNA oligonucleotides labeled by a pyrenylmethyl group at the 2'-sugar residue provide a useful tool for monitoring RNA hybridization. The present labeling method should be applicable to investigation of RNA structures.^[32]

Experimental Section

Synthesis of Pyrene-Modified RNA. Pyrene-modified oligoribonucleotides were synthesized by standard phosphoramidite chemistry using 5'-DMT-2'-(1-pyrenylmethyl)uridine phosphoramidite (DMT=4,4'-dimethoxytrityl).^[22] After removal of base and phosphate protective groups, the oligomers were purified with 20% denaturing polyacrylamide gel electrophoresis. The final deprotection of the 2'-blocking group (Fpmp=[1-(2-Fluorophenyl)-4-methoxypiperidinyl]) was done with HCl (0.1M) treatment. After neutralization, the solution was passed through a Sep-Pak C18 cartridge giving the desired oligonucleotides (8–10 O.D.; absorbance at 260 nm). The integrity of the purified oligonucleotides was verified with ion-spray mass-spectral analysis.

Physical Measurements. All measurements were carried out in Na₃PO₄ (10 mM) and NaCl (100 mM), adjusted to pH 7.0. Duplex melting curves were obtained at a common total strand concentration (4.3×10^{-5} M) containing a 1:1 molar ratio of oligonucleotides. Fluorescence spectra were obtained at an excitation wavelength of 338 nm. Fluorescence quantum yields were estimated at 23 °C on the basis of quinine sulfate in sulfuric acid (1.0N) as a standard.

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Versatile Approaches to the Polymer-Supported Synthesis of Bidentate Phosphorus-Containing Ligands

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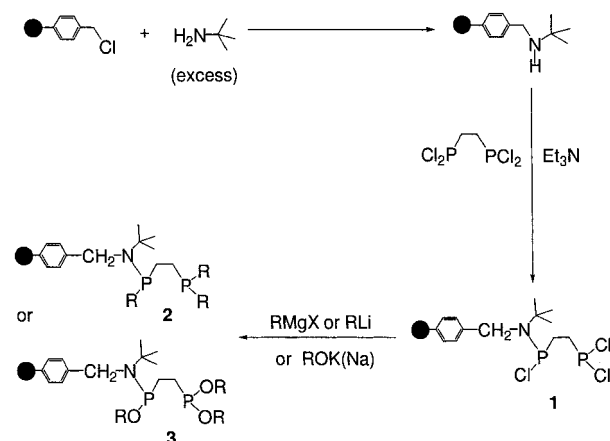
In recent years, combinatorial chemistry has been developed and applied by the pharmaceutical industry to rapidly synthesize and screen thousands of compounds in libraries for drug discovery and optimization.^[1,2] Combinatorial approaches have also led to the discovery of more efficient superconducting,^[3] photoluminescent,^[4] magnetoresistive,^[5] dielectric,^[6] and polymeric^[7] materials, and the development of heterogeneous catalysts.^[8] Moreover, promising results in the application of combinatorial methods to homogeneous

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catalysis spurred innovation in efficient synthetic and screening methods.^[9, 10] One potentially valuable approach is the combinatorial synthesis of homogeneous ligands using solid-supported methods.^[11] Bidentate phosphorus-containing ligands are especially important owing to the major role these ligands have played in the development of homogeneous catalysis.^[12] We report here the facile and rapid polymer-supported synthesis of novel diphosphane, phosphane–phosphinite, phosphane–thiophosphane, and phosphane–chlorophosphane ligands^[13] (abbreviated P–P ligands) to access a variety of ligand architectures for the combinatorial preparation of homogeneous catalysts.

The polymer-supported phosphane–aminophosphanes (substrates of Table 1) were straightforwardly synthesized (Scheme 1) by treating Merrifield's resin with excess *tert*-



Scheme 1. Synthesis of polymer-supported cleavable P–P ligands.

butylamine to form the polymer-supported secondary amine. This resin reacts with 1,2-bis(dichlorophosphanyl)ethane in the presence of triethylamine to give the polymer-supported precursor **1**. Only one phosphorus atom of bis(dichlorophosphanyl)ethane is linked to the resin probably due to steric impediments of the *tert*-butyl groups and the excess of diphosphane used. Reaction of the precursor **1** with a variety of organomagnesium halides, organolithium reagents, and metal alkoxides in THF at room temperatures led to complete substitution of P–Cl bonds. After filtration and washing with THF, H₂O, and hexane, the resins **2** and **3** with cleavable diphosphane or diphosphinite ligands were obtained. The formation of **1–3** was conveniently monitored by routine ³¹P NMR spectroscopy (Figure 1) and was judged complete based on the cleaved products (Table 1).

Cleavage of the P–P ligands from resin **2** proceeds selectively with PCl₃ at room temperature and with a variety of alcohols and thioalcohols^[14] in refluxing THF to generate the corresponding phosphane–chlorophosphanes (compounds **5** in Eq. (1)), phosphane–phosphinites,^[15] and phosphane–thiophosphanes (compounds **4** in Eq. (1)). Yields in Table 1 refer to products isolated by simple filtration, followed by removing solvents and excess cleavage reagent under vacuum and are referenced to the initial loading of the Merrifield resin. In all cases, the crude cleaved products were obtained with a high degree of purity (≥ 95 %) as ascertained

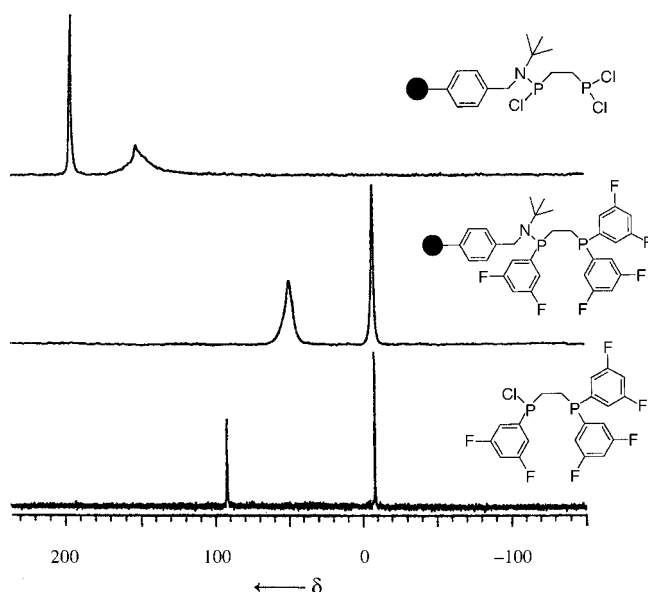
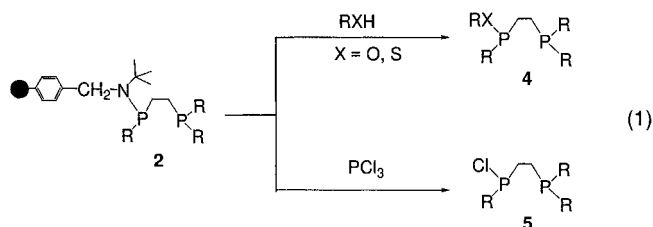


Figure 1. Routine 121-MHz ³¹P NMR spectra of a resin-supported P–P ligand precursor (top), the resin-supported diphosphane ligand (middle), and the cleaved phosphane–chlorophosphane (bottom).

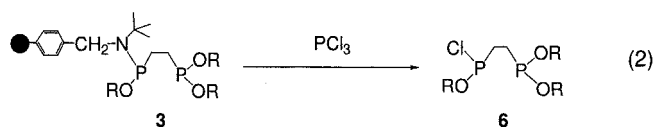


by ¹H/³¹P NMR spectroscopy (see Figure 1) and GC/MS. Known products were identified by comparison with ¹H/¹³C/³¹P NMR spectral data from literature and/or with data from authentic samples. New compounds were characterized by one- and two-dimensional ¹H/¹³C/³¹P NMR spectroscopy, high-resolution mass spectrometry, and other standard techniques.^[16]

Entries 1, 2, 7, and 9 in Table 1 illustrate substitutions with aliphatic Grignard compounds to obtain electron-rich P–P ligands, and entries 3–6 and 10–13 demonstrate formation of aromatic P–P ligands including compounds with electron-withdrawing substituents. Entry 14 shows clean and complete replacement of chloride by alkoxy groups in the presence of the alcohol and an inorganic or organic base. The cleavage of **2** furnishes the novel C₁ symmetric ligands in moderate yields. These kinds of ligands are difficult to prepare by standard solution chemistry.^[13] Examples for cleavage by RSH reagents are entries 8–10. Entries 11–13 further illustrate that polymer-supported ligands **2** can be employed to generate a phosphane–chlorophosphane which can be further modified with a variety of RMgX (the product of entry 12 is used for the reaction shown as entry 15), ROH, and amines.^[17] Interestingly, with P–N and P–O bonds present, PCl₃ regioselectively cleaves the P–N bond to afford phosphinite–chlorophosphinites **6** [Eq. (2)] (Table 1, entry 14), presumably due to the greater reactivity of the P–N bond. Cleavages of **2** on 13.6-g and 6.0-g scales (entries 3 and 12) generated 2.17 g (59 %) and

Table 1. Polymer-supported synthesis of P–P ligands.

Entry	Substrates 2 , 3	$\delta(^{31}\text{P})$	Product 4–6	$\delta(^{31}\text{P})$	Yield [%] (isolated)
1		52.2, –17.8		135.8, –18.2	51
2		45.5, –35.0		132.5, –33.5	24
3		47.1, –11.4		120.4, –11.6	59
4		46.2, –14.3		119.2, –14.0	27
5		45.4, –13.6		124.7, –13.4	30
6		48.3, –17.8		131.5, –17.7	30
7		48.3, –23.8		138.5, –23.0	26
8		47.1, –11.4		30.0, –11.8	31
9		63.4, 9.4		51.5, 9.9	53
10		47.6, –7.5		31.2, –9.0	71
11		31.9, –33.7		89.5, –33.0	75
12		49.2, –7.3		91.4, –8.7	74
13		33.0, –38.0		76.7, –38.3	57
14		182.1, 137.0		199.3, 178.9	56
15		49.2, –7.3		–8.4, –10.3	59



1.58 g (74%) of the cleaved phosphine–phosphinite and phosphine–chlorophosphane, respectively, illustrating the practicability of the present process.

The procedures reported here allow not only the synthesis of polymer-supported P–P ligands, but also their cleavage from the resin, thus making them available in solution. All separation and purification steps are simple filtrations and, given the ready availability of original reagents, the process is

amenable to library synthesis. Thus the cleavable compounds **1–3** are ideally suited for the rapid and regioselective synthesis of a variety of novel C_1 -symmetric P–P ligands. Applications of the resin-supported P–P ligands as well as of the cleaved ligands in catalysis will be reported later.

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Enantioselective Reduction of Ketones Catalyzed by Polymer-Supported Sulfonamide Using $\text{NaBH}_4/\text{Me}_3\text{SiCl}$ (or $\text{BF}_3 \cdot \text{OEt}_2$) as Reducing Agent**

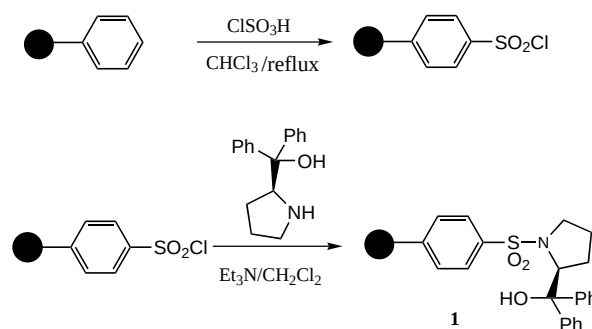
Jian-bing Hu, Gang Zhao,* and Zuo-ding Ding

The enantioselective reduction of ketones to form optically active secondary alcohols is a major area of research in organic chemistry, and a large number of reducing agents and chiral catalysts have been developed that facilitate this reaction under a wide range of conditions.^[1] One of the most successful reduction reactions involves the use of borane in

the presence of homogeneous catalysts derived from chiral amino alcohols.^[2] These catalysts often provide higher enantioselectivities than heterogeneous catalysts, but the development of efficient heterogeneous catalysts is still a challenging target, because workup of the reaction and the recovery of heterogeneous catalysts are more convenient than those of homogeneous catalysts. In the past decade, various groups have reported the preparation and application of heterogeneous catalysts for the enantioselective reduction of ketones,^[3] and several reducing agents were used: BH_3 ,^[4] NaBH_4 ,^[5] and LiAlH_4 .^[6] Of these reducing agents, BH_3 was most widely applied and gave the best results in the presence of polymer-supported chiral amino alcohols. However, only a few of the reducing agents displayed high reactivity and enantioselectivity owing to the diffusion limitations caused by the polymer matrix. Furthermore, the use of BH_3 as a reducing agent requires a lot of precautions because of its toxicity. It is therefore necessary to develop new reducing systems that can easily be employed and that give high enantiomeric excesses.

It has been reported that diborane can be generated by treating NaBH_4 with Me_3SiCl ^[7] or $\text{BF}_3 \cdot \text{OEt}_2$.^[8] Herein, to the best of our knowledge, we report the first asymmetric reduction of ketones by employing $\text{NaBH}_4/\text{Me}_3\text{SiCl}$ (or $\text{BF}_3 \cdot \text{OEt}_2$) as reducing agents, and polymer-supported chiral sulfonamide **1** as the catalyst (Scheme 1).

The two-step synthetic route to **1** is outlined in Scheme 1. In the first step, the polymer beads of polystyrene resin (2% divinylbenzene, 200–400 mesh) were treated with excess



Scheme 1.

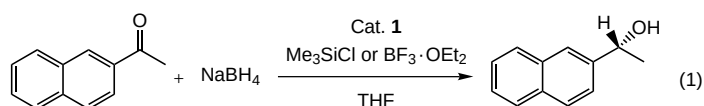
chlorosulfonic acid in refluxing chloroform to give the chlorosulfonylated polymer according to a literature procedure.^[9] This polymer was synthesized several times; the yield was typically 96%, and the degree of chlorosulfonylation determined by elemental analysis was 4.72 mmol Cl and 4.73 mmol S per gram of polymer. In the second step, (S)-diphenylprolinol was grafted onto the chlorosulfonylated polymer in the presence of Et_3N at room temperature over four days. After the reaction was complete, the insoluble chiral polymer **1** was isolated from the reaction mixture by filtration, and then thoroughly washed with water and methanol. Chiral polymer **1** was characterized by IR spectroscopy, which revealed the characteristic absorptions of the SO_2 group at 1154 and 1359 cm^{-1} , and by elemental analysis, which showed that the N content was 2.29 mmol per gram of **1**.

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To determine the best reaction conditions, we chose the reduction of β -acetoneaphthone as a model reaction [Eq. (1)],



and the results are shown in Table 1. We used THF as the solvent because the diborane produced can form a borane–THF complex.^[7] The reductions proceeded smoothly with

Table 1. Asymmetric reduction of acetoneaphthone under different reaction conditions.^[a]

Entry	Chiral polymer [mol %]	<i>T</i> [°C]	NaBH ₄ /Me ₃ SiCl Yield [%] ^[b]	NaBH ₄ /Me ₃ SiCl <i>ee</i> [%] ^[c]	NaBH ₄ /BF ₃ ·OEt ₂ Yield [%] ^[b]	NaBH ₄ /BF ₃ ·OEt ₂ <i>ee</i> [%] ^[c]
1	10	RT	99	9.7	98	0
2	10	reflux	n.d.	n.d.	99	80.3
3	15	reflux	98	89.2	99	95.3
4	20	reflux	99	93.1	98	94.5
5	25	reflux	98(97) ^[d]	96.3(89.5) ^[d]	n.d.	n.d.
6	30	reflux	98	95.5	n.d.	n.d.

[a] The solvent for acetoneaphthone was added by means of a syringe pump. The absolute configuration was determined to be *R* by comparison with the reported specific rotation (n.d. = not determined). [b] Yields of isolated products. [c] Determined by using chiral HPLC. [d] The solvent for acetoneaphthone was added with a dropping funnel.

both NaBH₄/Me₃SiCl and NaBH₄/BF₃·OEt₂ as reducing agents, and excellent yields were obtained under all the reaction conditions studied. The results given in Table 1 show that the level of enantiomeric excess is sensitive to the reaction temperature. As in similar cases, a decrease in the reaction temperature leads to a reduction of the stereoselectivity (Table 1, entries 1 and 2).^[4d, 5, 10] The enantioselectivity is significantly affected by temperature probably because of the increased flexibility of the chiral polymer and the better mobility of the substrates in the polymer at higher temperature, hence making the catalytic sites on the polymer beads more accessible to the substrates.

Apart from the reaction temperature, the ratio of the catalysts has an enormous impact on the reduction. As the amount of catalyst was progressively increased, the enantiomeric excess at first increased and then leveled out. The maximum *ee* levels of 96.3 % and 95.3 % for NaBH₄/Me₃SiCl or NaBH₄/BF₃·OEt₂, respectively, can be obtained with different catalyst ratios (Table 1, 25 % mmol and 15 % mmol, cf. entries 5 and 3, respectively). Adjidjonou and Caze reported similar effects in reductions using a polymer-supported catalyst.^[5]

To extend the scope of the reduction, we studied the reduction of other ketones under the optimum reaction conditions [Eq. (2)], and the results are summarized in

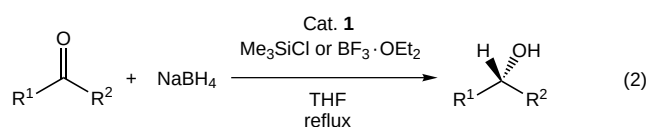


Table 2. Our reducing systems were highly efficient in the reduction of ketones. In all cases, the total conversion of the ketones into the corresponding alcohols was obtained in yields of more than 91 %. On the other hand, a significant variation in the *ee* values was observed, depending on the nature of the ketones. The two reducing systems were all especially effective in the reduction of aromatic ketones, but much less so in the reduction of the alkyl ketones. The *ee* value obtained in the reduction of aromatic ketones was as high as 96.6 %, whereas the maximum *ee* for the alkyl ketones was only 89.5 %. Furthermore, the reduction was affected by the electronic effects of the substituents on the phenyl ring. Interestingly, an electron-withdrawing group improved the reactivity and enantioselectivity. *p*-Methoxyacetophenone gave a lower reaction rate than *p*-nitroacetophenone: 3 h and 2 h, respectively, were needed for complete conversion. Furthermore, the *ee* values from the reduction of *p*-methoxyacetophenone were lower than those from *p*-nitroacetophenone (Table 2, 84 % and 96 %, cf. entries 3 and 4, respectively).

Table 2. Asymmetric reduction of ketones.^[a]

Entry	Ketone	NaBH ₄ /Me ₃ SiCl Yield [%] ^[b]	NaBH ₄ /Me ₃ SiCl <i>ee</i> [%] ^[c]	NaBH ₄ /BF ₃ ·OEt ₂ Yield [%] ^[b]	NaBH ₄ /BF ₃ ·OEt ₂ <i>ee</i> [%] ^[c]	Con-fig. ^[e]
1	acetophenone	98	95.7	98	95.1	<i>R</i>
2	<i>p</i> -bromoacetophenone	97	96.1	98	94.1	<i>R</i>
3	<i>p</i> -methoxyacetophenone	97	84.1	97	84.2	<i>R</i>
4	<i>p</i> -nitroacetophenone	99	96.6	98	96.0	<i>R</i>
5	α -chloroacetophenone	98	96.1	98	95.8	<i>S</i>
6	α -bromoacetophenone	99	96.6	98	94.0	<i>S</i>
7	α -tetralone	98	91.0	98	86.1	<i>R</i>
8	benzylacetone	97	65.1	98	64.5	<i>R</i>
8	1,1,1-triphenylacetone	96	89.5	95	87.0	<i>R</i>
9	1-cyclohexyl-1-propanone	95	71.1	96	69.8	<i>R</i>
10	2-butanone	91	50.6 ^[d]	92	47.5 ^[d]	<i>R</i>

[a] Experiments were performed on a 1 mmol scale. [b] Yields of isolated products after purification by column chromatography or by distillation. [c] Determined by using chiral HPLC. [d] Analytical samples were converted into 3-chlorophenylcarbamates.^[11] [e] The absolute configurations were determined by comparison with the reported specific rotations.

After the reduction was complete, the polymer-supported catalyst was easily removed by filtration. The catalyst was regenerated by first washing with refluxing methanol to eliminate the alcohol encapsulated in the polymer matrix, and then washing with hot water to remove the inorganic compounds formed in the reaction. Tests on the reduction of acetophenone (Table 3) show that the chiral polymer-supported catalyst can be recycled at least three times with little or no loss of performance.

Table 3. Recycling of chiral polymer (reduction of acetophenone).^[a]

Run	NaBH ₄ /Me ₃ SiCl Yield [%] ^[a]	NaBH ₄ /Me ₃ SiCl <i>ee</i> [%] ^[b]	NaBH ₄ /BF ₃ ·OEt ₂ Yield [%] ^[a]	NaBH ₄ /BF ₃ ·OEt ₂ <i>ee</i> [%] ^[b]
1	98	95.5	98	95.7
2	97	96.3	98	92.8
3	98	95.4	97	94.6

[a] Yields of isolated products. [b] Determined by using chiral HPLC.

In summary, we have clearly demonstrated that two kinds of reducing systems ($\text{NaBH}_4/\text{Me}_3\text{SiCl}$ or $\text{NaBH}_4/\text{BF}_3 \cdot \text{OEt}_2$) in combination with the new, chiral, polymer-supported *N*-sulfonamide **1** are effective in the reduction of prochiral ketones. The best *ee* values are obtained when the reduction is carried out in refluxing THF. The chiral polymer can be recovered easily and reused. The two reducing systems described should offer advantages over other reducing systems and thus find new applications.

Experimental Section

All reactions were carried out under nitrogen. THF was dried over sodium and freshly distilled before use. (*S*)-Diphenylprolinol was prepared according to a literature procedure.^[12] Cross-linked polystyrene resin (2%, 200–400 mesh) was obtained from Merck Company. The purity of all the reagents were checked by NMR spectroscopy.

Preparation of 1: Polymeric sulfonyl chloride (0.214 g, 1 mmol) was added to a solution of (*S*)-diphenylprolinol (1.016 g, 4 mmol) in CH_2Cl_2 (30 mL) and Et_3N (0.104 g, 1 mmol) at room temperature. The resulting mixture was stirred for four days. The polymer was then filtered off and washed successively with methanol, water, methanol/water (1:1), and methanol. After drying in vacuo at 50 °C for 5 h, the desired polymer (0.451 g) was obtained in approximately 96% yield.

General procedure for the asymmetric reduction of prochiral ketones using 1 and $\text{NaBH}_4/\text{Me}_3\text{SiCl}$: Me_3SiCl (0.132 mg, 1.2 mmol) was added to a suspension of NaBH_4 (45 mg, 1.2 mmol) in THF (10 mL). The suspension was heated at reflux and stirred for 1 h. Polymer-supported catalyst **1** (98 mg, 0.25 mmol) was added, and the reaction mixture was heated at reflux for a further 0.5 h. A solution of acetophenone (120 mg, 1 mmol) in THF (10 mL) was added at a rate of 3 mL h⁻¹ with a syringe pump. After the addition was complete, the mixture was treated with water and filtered. The polymer-supported catalyst was washed several times with EtOAc and water. The resulting aqueous solution was extracted with EtOAc (3 × 10 mL) and dried with MgSO_4 . The solution was evaporated and purified by silica-gel chromatography to give the pure product (120 mg, 0.98 mmol, 98%). $[\alpha]_D^{20} = +52.6$ ($c = 2.23$, CHCl_3). The optical yield was determined to be 95.7% by using chiralcel OJ column chromatography.

General procedure for the asymmetric reduction of prochiral ketones using polymer-supported catalyst 1 and $\text{NaBH}_4/\text{BF}_3 \cdot \text{OEt}_2$: $\text{BF}_3 \cdot \text{OEt}_2$ (0.254 mg, 1.8 mmol) was added to a suspension of NaBH_4 (46 mg, 1.2 mmol) in THF (10 mL). The suspension was heated at reflux for 0.5 h. Polymer-supported catalyst **1** (59 mg, 0.15 mmol) was added, and the reaction mixture was heated at reflux for a further 0.5 h. A solution of acetophenone (120 mg, 1 mmol) in THF (10 mL) was then added at a rate of 3 mL h⁻¹ with a syringe pump. After the addition was complete, the mixture was treated with water and filtered. The polymer-supported catalyst was washed several times with EtOAc and water. The resulting aqueous solution was extracted with EtOAc (3 × 10 mL) and dried with MgSO_4 . The solution was evaporated and purified by silica-gel chromatography to give the pure product (120 mg, 0.98 mmol, 98%). $[\alpha]_D^{20} = +52.4$ ($c = 1.01$, CHCl_3). The optical yield was determined to be 95.1% by using chiralcel OJ column chromatography.

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An Asymmetric Enzyme-Catalyzed Retro-Claisen Reaction for the Desymmetrization of Cyclic β -Diketones**

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The desymmetrization of prochiral compounds is of increasing importance in asymmetric synthesis because, in principle, quantitative yields with absolute optical purity may be obtained.^[1] Enzyme-catalyzed approaches to desymmetrization have, for the most part, involved the application of carbon–heteroatom hydrolases such as lipases and esterases.^[2] Reactions involving C–C bond cleavage are much rarer, although the group of Taschner was successful in applying an enzyme-catalyzed Baeyer–Villiger reaction to the desymmetrization of a variety of prochiral ketones.^[3] The desymmetrization of prochiral β -diketones by a retro-Claisen reaction has been reported using chiral bases, although diastereomeric and enantiomeric excesses were generally

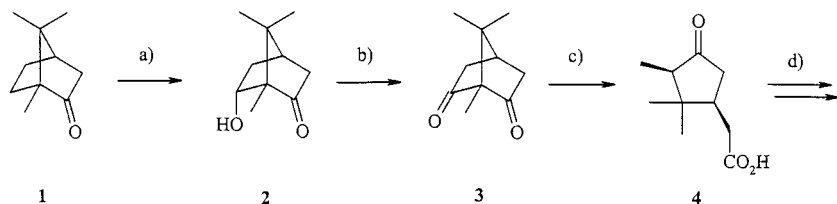
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poor and stoichiometric amounts of reagent were required.^[4] The class of enzymes required for hydrolysis of β -diketones, β -diketone hydrolases, (EC 3.7.1.X)^[5] have rarely been studied and only three have been purified to homogeneity. Of these, fumarylacetoacetate hydrolase from beef liver^[6] and aceto-pyruvate hydrolase from *Pseudomonas putida*^[7] have limited substrate ranges, in that they have been shown only to accept 3,5-diketo acids as substrates. No chiral transformations by these enzymes have been reported. We now report an enzymatic process for the desymmetrization of bicyclic prochiral β -diketones by employing a novel carbon–carbon bond hydrolase which we have named 6-oxocamphor hydrolase (6-OCH).

The starting point for this work involved the microbial degradation of (1*R*)-(+)-camphor (**1**) by *Corynebacterium* T1 (now deposited as *Rhodococcus* sp. NCIMB 9784), which was first described by the research group of Gunsalus (Scheme 1).^[8] One of the intermediates in the pathway is the symmetrical diketone **3** which undergoes cleavage in a retro-Claisen reaction to yield the keto acid **4**. The acid **4** was reported by the research group of Gunsalus to have a negative



Scheme 1. Metabolism of (1*R*)-(+)-camphor (**1**) by *Rhodococcus* sp. NCIMB 9784: a) cytochrome P450camr, b) alcohol dehydrogenase, c) 6-oxocamphor hydrolase, d) further metabolism.

optical rotation, and thus the degradation pathway can be envisaged to proceed from optically pure camphor through an achiral symmetrical intermediate **3** to another optically active metabolite **4** through a desymmetrization step. We decided to isolate the enzyme activity responsible for the conversion of **3** into **4** and define its substrate specificity with respect to other prochiral β -diketones.

The enzyme 6-oxocamphor hydrolase was isolated from *Rhodococcus* sp. NCIMB 9784 cultures grown on (1*R*)-(+)-camphor as the sole carbon source, which yielded approximately 40 units L⁻¹ of pure enzyme. The enzyme has now been purified to homogeneity, characterized biochemically, and the gene encoding the relevant protein cloned and sequenced. These data will be published elsewhere.

First the stereoselectivity of enzymatic hydrolysis of the natural substrate diketone **3** needed to be established. Diketone **3** was obtained by pyridinium chlorochromate oxidation^[9] of 6-*endo*-hydroxycamphor (**2**) obtained from extractions of the fermentation mother liquor. The pure enzyme was used to hydrolyze the symmetrical diketone **3** to the keto acid **4**, which was recrystallized from chloroform and its crystal structure determined by X-ray analysis (Figure 1). Refinement of the flack parameter suggested that the C2 carbon center was of the *R* configuration and the C4 center of the *S* configuration, although the standard deviation was rather high.^[10] However, statistical analysis of the 200 most

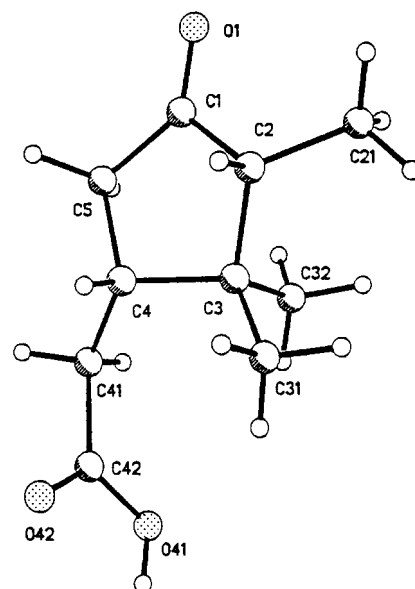
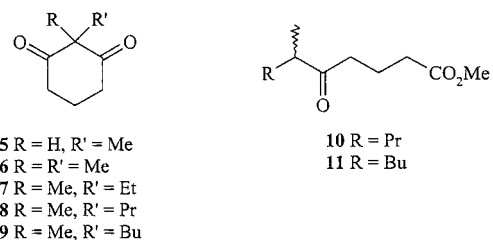


Figure 1. Crystal structure of (2*R*,4*S*)-campholinic acid (**4**) derived from enzymatic hydrolysis of 6-oxocamphor (**3**) by 6-oxocamphor hydrolase.

enantioselective reflections supported this assignment of absolute configuration. The enantiomeric excess of **4** was determined to be greater than 95% by chiral-shift NMR analysis of the methyl ester. Use of 10 mole % of [Eu(hfc)₃] allowed successful discrimination in the signals of one of the geminal methyl groups at C3 of the racemate. NMR spectroscopy also indicated the presence of the (2*S*,4*S*) diastereomer of **4** in a ratio of 1:6 to the predominant (2*R*,4*S*) product **4**. It should be noted that chemical hydrolysis of **3** with aqueous hydrochloric acid yielded the same mixture of *cis* and *trans* isomers as a racemate. Thus, whilst the C4 configuration is clearly determined by enzymatic specificity, it is likely that the C2 configuration is under thermodynamic control.

The substrate range of the enzyme was explored with a variety of β -diketones, including **5–9**; thin layer chromatography was applied to detect the evolution of product. None of



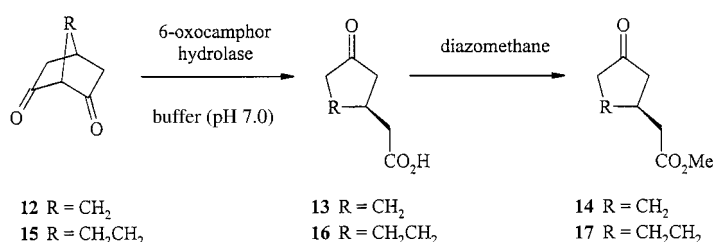
the acyclic diketones (pentane-2,5-dione and 3,3-dimethylpentane-2,5-dione) nor the simple monocyclic diketones (cyclohexane-1,3-dione, 5,5-dimethylcyclohexane-1,3-dione, 2-acetylcyclopentanone, 2-acetylcyclohexanone, and 2-methylcyclohexane-1,3-dione (**5**)) that were tested were substrates. On the other hand, other α,α -disubstituted cyclohexane diones, such as 2-methyl-2-ethylcyclohexane-1,3-dione (**7**),

2-methyl-2-propylcyclohexane-1,3-dione (**8**), and 2-methyl-2-*n*-butylcyclohexane-1,3-dione (**9**), resulted in hydrolysis by the enzyme.

Preparative scale transformations (with amounts of 0.5 mmol) of diones **8** and **9** led to keto acid products **10** and **11**, which were racemic. Thus, it may be that stereo-differentiation by the enzyme is poor in these cases, or that the inherent enantioselectivity of the process is masked by a subsequent nonenantioselective and perhaps nonenzymatic step.

The observed requirement for α,α -disubstituted β -diketones may be due to steric effects important for enzyme binding or activation due to a requirement for nonenolizable β -diketones. To probe these ideas further, the demethyl analogues of **3**, the diones **12** and **15**^[11] were prepared. Compounds such as **12** are well known to be nonenolizable due to ring strain (Bredt's rule). The synthesis of **12** was achieved by tetrapropylammonium perruthenate (TPAP) oxidation^[12] of 6-*endo*-hydroxynorbornanone, which was itself synthesized using the method of Werstiuk and Kadai.^[13]

When subjected to the same reaction conditions as employed for the enzymatic hydrolysis of **3**, diketones **12** and **15** were transformed into keto acids **13** and **16** (Scheme 2). The



Scheme 2. Hydrolysis of bicyclic ketones **12** and **15** by 6-oxocamphor hydrolase from *Rhodococcus* sp. NCIMB 9784.

methyl ester **14** was prepared (by treatment with diazomethane) and analysis of the product with chiral GC indicated an *ee* value of 84%. The absolute configuration of **14** was established as *S* by comparison of its sign of optical rotation with the literature value.^[14] It should be noted that **12** was hydrolyzed completely to **13** in buffer over a period of two hours, and thus the measured optical purity of **14** may have been lowered by background chemical hydrolysis of the diketone substrate.

The larger ethylene bridge in **15** made this compound more stable and, thus, background hydrolysis was negligible. After complete hydrolysis to keto acid **16**, the methyl ester **17** of the product was prepared (overall yield for two steps: 91%) and was assigned the *S* configuration by comparison of the sign of the optical rotation obtained with the literature value.^[15] The *ee* value was determined by comparative ¹³C NMR spectroscopy of the acetals formed from the racemate and the enzymatic product with (2*R*,3*S*)-butane-2,3-diol, and it was found to be 94%.

We have described the application of a novel enzymatic activity for the desymmetrization of three prochiral bicyclic β -diketones **3**, **12**, and **15**. The initial results with unsubstituted bicyclic diketones **12** and **15** are highly encouraging; good

stereoselectivities and access to useful chiral intermediates are obtained. For example, chiral cyclopentanones of type **13** are potential intermediates in the synthesis of natural products such as the jasmonic acids.^[16] Current studies are directed toward extending the substrate range of the enzyme and incorporating the chiral cycloalkanone products into asymmetric synthesis.

Experimental Section

Spectral data for norbornane-2,6-dione (**12**): IR (Nujol): $\bar{\nu}_{\text{max}}$ = 1751 cm⁻¹, 1774 cm⁻¹; ¹H NMR (250 MHz; CDCl₃): δ = 2.08 (m, 1H), 2.17 (m, 1H), 2.24 (m, 2H), 2.39 (m, 1H), 2.48 (m, 1H), 3.20 (m, 2H); ¹³C NMR (63 MHz; CDCl₃): δ = 32.9 (CH), 38.1 (CH₂), 43.3 (CH₂), 69.0 (CH), 206.2 (C=O); HR-MS: *m/z* calcd: 124.05243; found: 124.05242.

Purification of 6-oxocamphor hydrolase: The enzyme used for biotransformations (6-oxocamphor hydrolase, 6-OCH) was purified from a 10-L fermentation of *Rhodococcus* sp. NCIMB 9784 grown on (1*R*)-(+)-camphor as the sole carbon source. Wet cell paste (40 g) from the fermentation was disrupted using a Type KDL Dynomill, and, after removal of cell debris by centrifugation, a 40–80% ammonium sulfate cut of the cell supernatant was obtained. Sequential chromatography of the sample over Phenyl Sepharose, Fast Flow Q Sepharose, and Phenyl Superose on fast phase liquid chromatography (FPLC) resulted in 5% yield of pure 6-OCH that was homogeneous as judged by sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE). During chromatography, fractions containing 6-OCH were identified by spectrophotometric assay based on the decrease in absorbance at 294 nm of the native substrate, 6-oxocamphor (**3**). Using this assay, the specific activity of the pure protein was determined to be 357 U per mg of protein (where 1 U is 1 μ mol of substrate converted per minute).

Preparative scale enzymatic hydrolysis of diketones **3**, **12**, and **15**: 6-oxocamphor hydrolase (100 U) was added to a stirred solution of diketone **3**, **12**, or **15** (0.5 mmol) in 100 mM potassium phosphate buffer (pH 7.0, 50 mL) at room temperature. Thin layer chromatography analysis suggested completion of the reaction after 10 min (for **3**), 2 h (for **12**), and 24 h (for **15**). The mixture was acidified to pH 3.0 with dilute HCl and then extracted into ethyl acetate. After drying over MgSO₄, the solvent was removed and the crude carboxylic acid converted into its methyl ester using diazomethane. Isolated yields of the methyl ester of **4** and of **14** and **17** were 86%, 25%, and 91% respectively. Spectroscopic data for **14**^[13] and **17**^[15] were in agreement with the literature.

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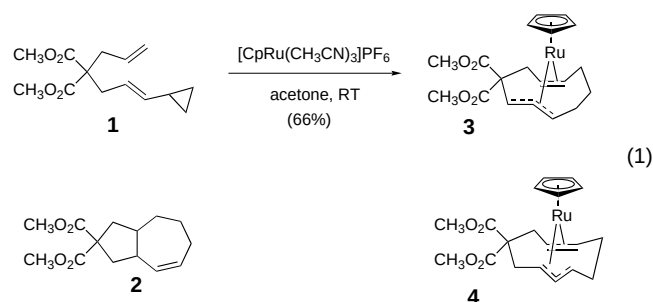
Synthesis of the First (1-3:6,7- η -Cyclodecadienyl)ruthenium Complex by the Intramolecular Reaction of an Alkene and a Vinylcyclopropane**

Barry M. Trost* and F. Dean Toste

The development of cyclization methods constitutes a continuing challenge because of the ubiquitous occurrence of cyclic structures, especially among bioactive targets. Improving synthetic efficiency by expanding the cycloaddition type protocols, especially to rings that cannot be formed by Diels–Alder type methods, and facilitating formation of unusual ring sizes, notable medium and large rings, then represent two significant objectives. Transition metal catalysis plays a major role towards meeting these objectives. In developing cyclization strategies^[1] centered around $[\text{CpRu}(\text{CH}_3\text{CN})_3]\text{PF}_6$ ^[2] as a catalyst, we have discovered an unprecedented reaction that led to the formation of a novel organometallic complex in which a medium-sized carbocycle was effectively created—a result that stands in sharp contrast to the Rh chemistry.

We have recently reported that $[\text{CpRu}(\text{CH}_3\text{CN})_3]\text{PF}_6$ ^[2] catalyzes the intramolecular [5+2] cycloaddition of alkynes

and vinylcyclopropanes.^[3] To establish the scope and limitations as well as compare the Ru catalyst to the highly successful Rh system developed by the Wender group,^[4] we investigated the extension of the ruthenium-catalyzed reaction to alkenes and vinylcyclopropanes. Reaction of diene **1** with 10% $[\text{CpRu}(\text{CH}_3\text{CN})_3]\text{PF}_6$ in acetone did not produce any of the desired [5+2] adduct **2**, but produced a small amount of an unknown ruthenium complex along with recovered diene. By carrying out the reaction of **1** with 0.5 equivalents of $[\text{CpRu}(\text{CH}_3\text{CN})_3]\text{PF}_6$, we were able to isolate an air-stable ruthenium complex in 66% yield [Eq. (1)].^[5]



Analysis of the ¹H NMR spectrum of the complex indicated that the product possessed a cyclopentadienyl moiety and a second ligand derived from **1**. Notably, the spectrum showed that the methoxycarbonyl groups were no longer equivalent and that the ligand derived from **1** had one proton less than the starting diene. Based on the ¹H and ¹³C NMR data and the structure of the substrate **1**, we tentatively assigned the structure of the unknown complex as the (1-3:7,8- η -cyclodecadienyl)ruthenium complex **4**. However, since we could not find previous examples of η^5 -cyclodecadienyl^[6] complexes, it was difficult to confirm the structure. Gratifyingly, we were able to grow crystals of the complex suitable for X-ray structure analysis.^[7] X-ray analysis concretely established the structure as the (1-3:6,7- η -cyclodecadienyl)ruthenium complex **3** (Figure 1).

Complex **3** has a distorted octahedral structure with the two η^2 -olefin carbon atoms and the terminal carbon atoms of the η^3 -allyl moiety occupying one plane. The η^2 -olefin is situated *endo* and the cyclopentadienyl ligand *exo* with respect to the η^3 -allyl group. Similar geometry is found in (arene)ruthenium-(1-3:5,6- η -cyclooctadienyl) complexes.^[6a,e] Despite the presence of a quaternary carbon atom adjacent to C1,^[8] the η^3 -allyl moiety and η^2 -olefin in complex **3** are essentially symmetrically bound to the ruthenium center. This symmetry is also similar to that of the neutral complex $[\text{Ru}(1-3:6,7-\eta\text{-cod})(\eta^5\text{-pyrrole})]$,^[6a] but differs from that of the cationic complex $[\text{Ru}(1-3:5,6-\eta\text{-cod})(\text{cot})]^+$ which shows a difference of 0.25 Å in the ruthenium–allyl terminal carbon bond lengths (cod = 1,5-cyclooctadienyl; cot = cyclooctatriene).^[6b] The sp³-carbon atoms adjacent to the π -allyl group are placed *exo* to the allyl plane, with the quaternary carbon atom C(10) having a greater displacement. The deviation from planarity is only slightly less than observed in the $[\text{Ru}(1-3:5,6-\eta\text{-cod})]$ complexes. However, the olefin in complex **3** is essentially planar

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

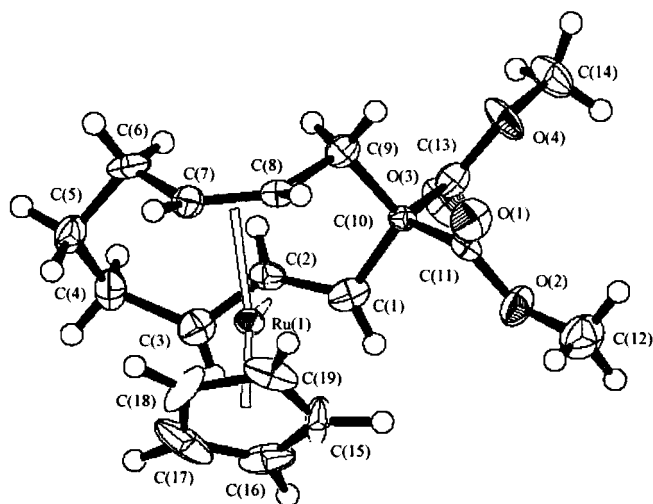
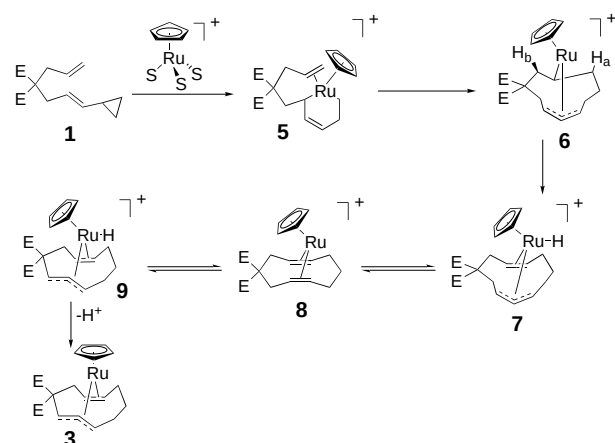


Figure 1. ORTEP drawing of complex **3**. Selected bond distances [Å], bond angles [°], and torsion angles [°] (see Supporting Information): Ru(1)–C(1) 2.172(6), Ru(1)–C(2) 2.128(5), Ru(1)–C(3) 2.195(5), Ru(1)–C(7) 2.177(5), Ru(1)–C(8) 2.160(5), C(1)–C(2) 1.424(9), C(2)–C(3) 1.363(12), C(7)–C(8) 1.424(7); C(2)–Ru(1)–C(8) 84.2(1), Ru(1)–C(1)–H(1) 89.8, Ru(1)–C(2)–H(2) 130.8, Ru(1)–C(3)–H(3) 80.9, Ru(1)–C(1)–C(10) 111.2(4), Ru(1)–C(3)–C(4) 121.3(4), C(1)–C(2)–C(3) 128.0(6), C(6)–C(7)–C(8) 131.7(6), C(7)–C(8)–C(9) 127.7(5); C(10)–C(1)–C(2)–C(3) 23.4(6), C(1)–C(2)–C(3)–C(4) –13.0(5), C(6)–C(7)–C(8)–C(9) –5.4(9).

(torsion angle 5.4(9)°), which is different from that observed in [Ru(1-3:5,6- η -cod)(η^5 -pyrrole)]^[6a] (torsion angle 23.9(9)°). Presumably, the planar olefin and the five sp²-carbon atoms are better accommodated by the larger ring size of **3**.

A mechanistic rationale for the formation of **3** is detailed in Scheme 1. The reaction is proposed to be initiated by conversion of the vinylcyclopropane into the ruthenacyclohexene **5**. Our previous results in the ruthenium-catalyzed [5+2] cycloaddition of alkynes and vinylcyclopropanes^[3] are consistent with the initial formation of a ruthenacyclopentene rather than a ruthenacyclohexene **5**. However, the mechanism outlined in Scheme 1 suggests that, in the absence of a π -unsaturation with high coordinating ability like an alkyne, coordinatively unsaturated ruthenium(II) can rearrange a vinylcyclopropane into a ruthenacyclohexene. A similar



Scheme 1. Mechanistic hypothesis for the formation of complex **3**. Open coordination sites on the ruthenium centre in any of the proposed intermediates may be occupied by the solvent (acetone) or acetonitrile. E = CO₂CH₃; S = solvent.

reaction has been proposed as an alternative mechanism for the rhodium-catalyzed [5+2] cycloaddition of alkenes and vinylcyclopropanes.^[4e] Ruthenacyclohexene **5** can undergo a 7-endo-trig carbathenation of the olefin to generate the 16-electron π -allylruthenium(IV) complex **6**. This coordinatively unsaturated complex is ideally suited for *syn*- β -hydrogen elimination of H_a to generate π -allylruthenium(IV) hydride **7**. Presumably, β -hydrogen elimination of H_b does not occur since the required geometry cannot be readily accessed. Reductive elimination of the hydride in **7** generates the coordinatively unsaturated 16-electron ruthenium(II) complex **8**. Insertion into the allylic C–H bond of the symmetrical diene generates η^3 -allylruthenium hydride **9**. Deprotonation of **9** or hydrogen atom transfer^[9] from **8** to acetone or diene **1** generates neutral [CpRu(1-3:6,7- η -cyclodecadienyl)] **3**. While other pathways, such as ones involving a series of metal-initiated cationic rearrangements, exist, the one proposed appears most reasonable at the present based upon known types of behavior.^[10]

In conclusion, we have prepared the first (1-3:6,7- η -cyclodecadienyl)metal complex from the intramolecular reaction of alkenes and vinylcyclopropanes with [CpRu(CH₃CN)₃]PF₆. A mechanism involving the conversion of the vinylcyclopropane into a ruthenacyclohexene and allylic C–H activation of a 1,6-cyclodecadiene is proposed.^[1d] This unusual reactivity highlights the divergence in behavior between the Ru and Rh catalysts in their reactions with vinylcyclopropanes. The reaction also provides a novel entry into 10-membered rings.^[11] Efforts to further understand the mechanism and to exploit the reaction for the catalytic formation of 10-membered rings are ongoing.

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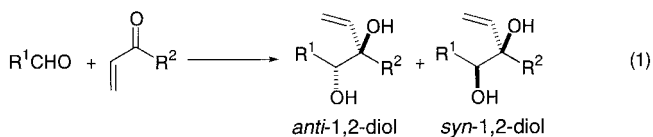
- 1 H), 1.88 (m, 1H), 1.81 (dd, $J = 13.4$, 6.2 Hz, 1H), 1.76 (dd, $J = 14.0$, 8.6 Hz, 1H), 1.42–1.22 (m, 2H), 1.13 (q, $J = 12.3$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 171.5$, 171.2, 86.2, 85.2, 84.7, 74.0, 57.3, 52.5, 52.5, 51.4, 49.3, 47.1, 34.3, 24.2, 22.0.
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Stereoselective Cross Pinacol-Type Coupling between α,β -Unsaturated Ketones and Aldehydes Mediated by Chromium(II) and R_3SiCl **

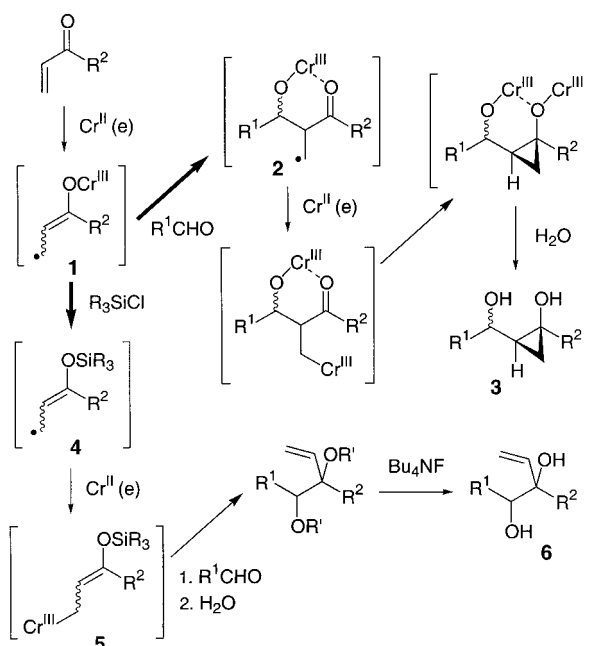
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The Pinacol-type coupling of aliphatic carbonyl compounds to form 1,2-diols is an attractive and promising tool for organic synthesis.^[1, 2] In contrast to the case of aromatic carbonyl compounds, reagents for the coupling of aliphatic aldehydes are limited, and intermolecular cross coupling of two carbonyl compounds in a selective manner is especially difficult. We

report herein the cross pinacol-type coupling reaction between an α,β -unsaturated ketone and an aldehyde mediated by chromium(II) and R_3SiCl [Eq. (1)].



Aldehydes are usually unreactive to chromium(II) because of its moderate reducing ability. However, reactions promoted by a one-electron transfer from chromium(II) proceed with some carbonyl compounds, such as α,β -unsaturated aldehydes and ketones.^[3, 4] In the first step of these reactions, a radical enolate **1** is formed (Scheme 1). When the reaction is



Scheme 1. Mechanism of the coupling reactions; R = Me or Et, R' = SiR_3 or H.

conducted in the presence of an aldehyde under anhydrous conditions, an intermolecular aldol reaction, which leads to **2**, is followed by a cyclopropanation reaction to give the *cis*-hydroxyalkyl-substituted cyclopropanol **3**.^[4] In contrast, we have found that the reaction course changes dramatically with the addition of Me_3SiCl , producing cross-pinacol coupling products 1,2-diols **6**, after desilylation with Bu_4NF . For example, a mixture of 5-phenyl-1-penten-3-one (**7**, 2.0 equiv) and nonanal (1.0 equiv) in *N,N*-dimethylformamide (DMF) was added at 25 °C to a mixture of CrCl_2 (8.0 equiv) in DMF in the presence of Me_3SiCl (6.0 equiv), and the resulting mixture was stirred at 25 °C for 1 h. After workup with water followed by desilylation with Bu_4NF , 1-vinyl-substituted 1,2-diols **8** were obtained in almost quantitative yield (*anti/syn* = 40:60).

The key factor that leads to the cross pinacol-type coupling reaction is the fast trapping of an enolate with Me_3SiCl leading to a trimethylsiloxy compound.^[5] Therefore, when the

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reduction of an α,β -unsaturated ketone with chromium(II) is conducted with Me_3SiCl , the radical enolate **1** will be trapped with Me_3SiCl to give the γ -siloxy-substituted allylic radical **4**. Such an allylic radical **4** can be reduced easily with chromium(II) to afford the corresponding allylic chromium species **5**.^[6–9] Because the process is performed in the presence of an aldehyde,^[10] a coupling reaction takes place between the γ -siloxy-substituted allylic chromium complex **5** and the aldehyde. The coupling reaction leading to 1,2-diols **6** proceeds with Me_3SiCl , Et_3SiCl , Me_2SiCl_2 , and PhMe_2SiCl ; however, the addition of $t\text{BuMe}_2\text{SiCl}$ or $i\text{Pr}_3\text{SiCl}$ to the mixture does not afford the desired coupling products, probably owing to the slow trapping process of the chromium enolate with R_3SiCl .

The *anti/syn* ratio changed only slightly when using different substituents R of R_3SiCl .^[11] On the other hand, the reaction temperature influenced the ratio dramatically. At 0 °C, the *anti*-1,2-diol **8a** was produced selectively in a ratio of 93:7,^[12] but at higher temperatures the *anti/syn* ratio decreased gradually (Table 1), and the *syn* adduct **8b** was obtained as a major product at 75 °C in an *anti/syn* ratio of 10:90.

The results obtained with several kinds of α,β -unsaturated ketones and aldehydes are summarized in Table 2. Substituents on the carbon–carbon double bonds of the enones slowed down the reaction. Although α -substituted enones gave pinacol adducts in good yields (Table 2, entries 5 and 6), β -substituted enones did not afford the desired product. The diastereoselectivity also showed a similar temperature dependence to that described above, with the proportion of *syn* adduct increasing with increasing temperature. In contrast, reactions using 2-methylenecycloheptanone gave an *anti* adduct exclusively, irrespective of the reaction temperature

Table 1. Effects of reaction temperature on the diastereomeric ratios of cross pinacol-type reactions.^[a]

<i>T</i> [°C]	0	10	20	30	40	50	60	75
Time [h]	5	2	1	1	0.5	0.5	0.25	0.25
Yield [%]	99	97	96	93	90	86	84	85
<i>anti:syn</i> ^[b]	93:7	78:22	64:36	45:55	36:64	23:77	19:81	10:90

[a] The reactions were conducted on a 1.0-mmol scale. 5-Phenyl-1-penten-3-one (**7**, 2.0 mmol), CrCl_2 (8.0 mmol), and Et_3SiCl (6.0 mmol) were used per mmol of nonanal ($\text{R}^1 = n\text{-C}_8\text{H}_{17}$, $\text{R}^2 = \text{Ph}(\text{CH}_2)_2$). [b] Diastereomeric ratios were determined by isolation and/or by ^1H NMR spectroscopy.

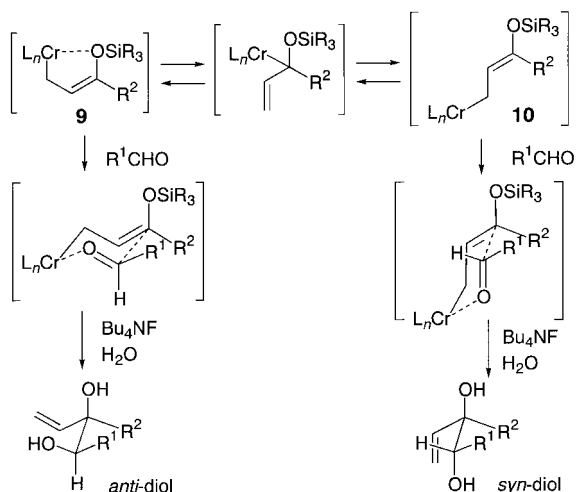
(Table 2, entry 6). To reduce the amount of chromium salt used in the reaction, we attempted a catalytic reaction using manganese as a reductant^[5, 13] of chromium(III). The reaction proceeded almost quantitatively at 25 °C; however, the yields decreased and the *anti/syn* ratios were not improved at either 0 or at 75 °C (Table 2, entry 2).

The addition of allylic chromium reagents to carbonyl compounds usually proceeds via a six-membered transition state with a chair form, and the diastereoselectivity reflects the configuration of the allylic chromium species (Scheme 2).^[14, 15] The formation of only the *anti* product from 2-methylenecycloheptanone, irrespective of the reaction temperature, suggests that the diastereoselectivity of the reaction also depends on the stereochemistry of the γ -siloxyallylic

Table 2. Formation of cross pinacol-type 1,2-diols from α,β -unsaturated ketones and aldehydes.^[a]

Entry	R^1	Enone	Time [h]	0 °C		<i>anti/syn</i> ^[b]	75 °C		<i>anti/syn</i> ^[b]
				Yield [%]			Yield [%]		
1	$n\text{-C}_8\text{H}_{17}$		5	99		93:7	0.25	85	10:90
2	$n\text{-C}_8\text{H}_{17}$	7	24	64 ^[c]		70:30	6	42 ^[c]	29:71
3	$c\text{-C}_6\text{H}_{11}$	7	5	98		60:40	0.25	80	19:81
4	$\text{Ph}(\text{CH}_2)_2$		5	72		> 99: < 1	0.5	52	59:41
5	$n\text{-C}_8\text{H}_{17}$		24	44		79:21	2	61	10:90
6	$\text{Ph}(\text{CH}_2)_2$		4	94 ^[d]		> 99: < 1	0.25	80 ^[d]	> 99: < 1

[a] The reactions were conducted on a 1.0-mmol scale. α,β -Unsaturated ketone (2.0 mmol), CrCl_2 (8.0 mmol), and Et_3SiCl (6.0 mmol) were used per mmol of aldehyde. [b] Diastereomeric ratios were determined by isolation and/or ^1H NMR spectroscopy.^[12] [c] CrCl_2 (0.8 mmol), Mn (4.0 mmol), and Et_3SiCl (6.0 mmol) were used per mmol of aldehyde. [d] Methylenecycloheptanone (4.0 mmol), CrCl_2 (16 mmol), and Et_3SiCl (12 mmol) were employed per mmol of aldehyde.



Scheme 2. Mechanism for diastereoselectivity.

chromium compounds formed, by virtue of which 2-methylenecycloheptanone can only form the *cis* isomer.

In the case of γ,γ -disubstituted allylic chromium species with a γ -siloxy group, the equilibrium between **9** and **10** is more quickly established^[17] than for γ,γ -dialkyl-substituted allylic species.^[14b] There are two possible reasons that account for the temperature dependence. One is a shift in the equilibrium from **9** to **10** by increasing the temperature.^[18] The other is that the addition rate of **10** to aldehydes could be increased more by temperature than that of **9**.^[19] In both cases, the mechanism also suggests that the equilibrium between **9** and **10** shifts to the *cis* isomer **9** when R² becomes bulkier. For example, the proportion of *anti*-diol derived from **9** was increased in the case of cyclohexyl vinyl ketone (Table 2, entry 4) as expected.

Experimental Section

8 (Table 2, entry 1, 0 °C): Et₃SiCl (1.0 mL, 6.0 mmol) was added to a mixture of CrCl₂ (0.98 g, 8.0 mmol; 99.9% purity, Aldrich) in dry, oxygen-free DMF (15 mL; Wako Pure Chemicals), and the mixture was stirred for 30 min. The mixture was cooled to 0 °C, and a solution of nonanal (0.14 g, 1.0 mmol) and 5-phenyl-1-penten-3-one (**7**, 0.32 g, 2.0 mmol) in DMF (5 mL) was added at 0 °C. After stirring for 5 h at 0 °C, the reaction mixture was poured into water (20 mL). The mixture was extracted with diethyl ether (3 × 20 mL), and the organic extracts were dried over anhydrous magnesium sulfate and concentrated. The crude mixture was diluted with THF (10 mL) and treated with a solution of Bu₄NF in THF (1.0 M, 4.0 mL) at 25 °C for 10 min, and then poured into water (5 mL). The mixture was extracted with diethyl ether (3 × 20 mL), and the organic extracts were dried over anhydrous magnesium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate 50:1) gave 3-(2-phenylethyl)-1-dodecene-3,4-diols **8** in 99% yield (0.99 mmol, *anti/syn* = 93/7).^[20]

8 (Table 2, entry 1, 75 °C): The mixture was heated at 75 °C before the addition of a solution of nonanal (0.14 g, 1.0 mmol) and **7** (0.32 g, 2.0 mmol) in DMF (5 mL).

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Ligand-Controlled Chemoselectivity in the Classical Oxidative Addition Reactions of MeI and Aldehydes to Rhodium(I) Complexes**

Roman Goikhman and David Milstein*

Rhodium(I) phosphane complexes are widely used in industrial and laboratory processes owing to their catalytic properties and high reactivities, particularly in oxidative addition reactions.^[1a] We report here a remarkable difference in the reactivity of similar alkylphosphane-rhodium(I) complexes bearing triflate and chloride ligands in classical oxidative addition reactions of aldehydes and MeI. High chemoselectivity in oxidative addition can be achieved by the choice of complex.

[[$(iPr_3P)_2RhOTf$] (**1**) ($OTf = OSO_2CF_3$, triflate) was synthesized by a simple procedure involving chloride abstraction from [[$(iPr_3P)_2RhCl$]₂] (**2**)^[2] with Me_3SiOTf , according to our reported method;^[3] an alternative synthesis has also been described.^[4] Complex **1** was characterized by X-ray structure analysis, which confirmed that the geometry around the metal is square planar, and that an η^2 -bound triflate ligand is present (Figure 1).^[5] The structure is similar to that of another rhodium η^2 -triflate complex.^[4] Surprisingly, η^2 coordination of the triflate ligand in mononuclear late transition metal complexes was not reported until 1998, and the reactivity of these uncommon complexes has yet to be examined.^[4, 6]

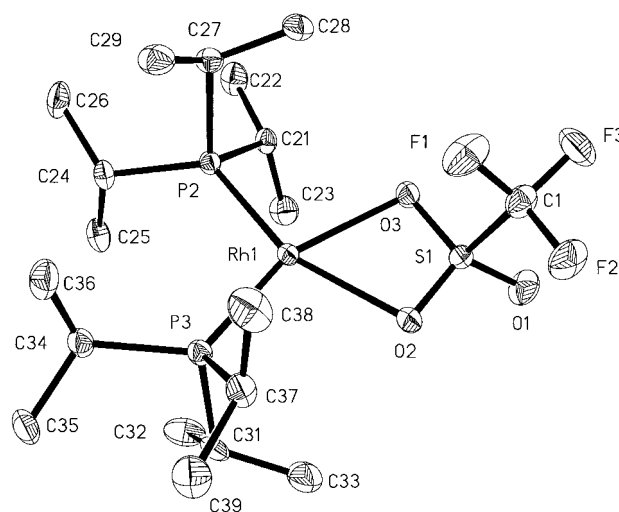


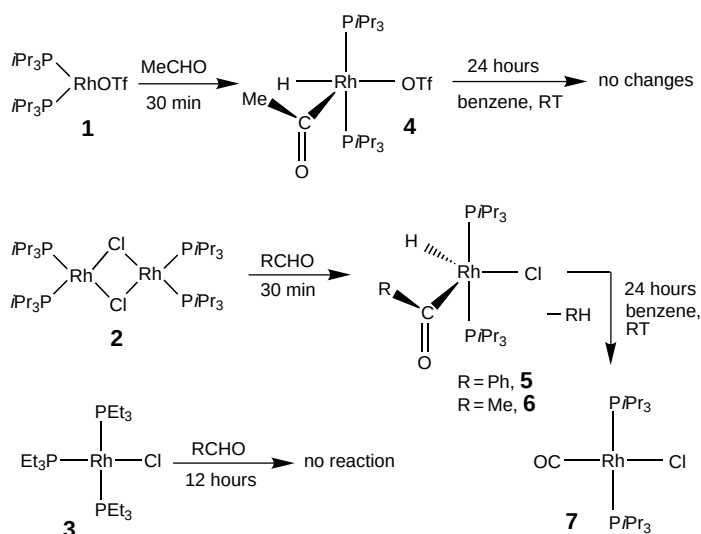
Figure 1. Structure of **1** (ORTEP plot; hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: Rh1–O3 2.283(2), Rh1–O2 2.265(3), Rh1–P3 2.2099(11), Rh1–P2 2.2143(11); P3–Rh1–P2 105.41(4), P3–Rh1–O2 95.78(7), P2–Rh1–O2 158.82(7), P2–Rh1–O3 95.38(7), P3–Rh1–O3 158.96(7), O2–Rh1–O3 63.48(9).

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We studied the oxidative addition reactions of **1** to probe the influence of the η^2 -bound triflate ligand on the reactivity of Rh^{I} compared to common chloro complexes such as **2** and $[(\text{Et}_3\text{P})_3\text{RhCl}]$ (**3**).^[7] The oxidative addition of aldehydes to rhodium(I) is an important reaction which plays a key role in catalytic processes such as the decarbonylation of aldehydes and hydroacylation of olefins.^[1a] However, examples of acylrhodium–hydride complexes resulting from the addition of simple aldehydes to Rh^{I} centers are rare,^[8–11] particularly because of the tendency of these complexes to undergo decarbonylation.^[1b]

The oxidative addition of acetaldehyde to **1** results in the quantitative formation of the new acylrhodium–hydride complex **4** (Scheme 1).^[12] X-ray structure analysis of **4** shows



Scheme 1. Reactions of Rh^{I} complexes with aldehydes.

a square-pyramidal geometry in which the acyl ligand adopts the apical position (Figure 2).^[5] Interestingly, the close analogue of **4**, namely compound **5** (Scheme 1), was reported to have a trigonal-bipyramidal structure.^[11] The H-Rh-OTf angle of **4** is 169° and the MeC(O)-Rh-OTf angle is 103° , whereas the H-Rh-Cl and PhC(O)-Rh-Cl angles of **5** are 128° and 147° , respectively. It is worth noting that the Rh-H bond in **4** ($1.46 \text{ \AA}$), located *trans* to the triflate ligand, is much shorter than that in **5** ($1.77 \text{ \AA}$).

Based on theoretical calculations, it was proposed that in $d^6 \text{ML}_5$ complexes, a π -donating chloride ligand (e.g. the chloride of **5**) causes an orbital orientation towards a trigonal-bipyramidal structure.^[11, 13] In the case of **4**, the triflate ion apparently has a negligible π -donating effect. The different structures of the closely related compounds **4** and **5** support the significant influence of π donation on the configuration of unsaturated Rh^{III} complexes.

The difference in the configurations of **4** and **5** is reflected in their reactivities. Whereas complex **5** and the analogous acetaldehyde adduct **6**^[12, 14] undergo decarbonylation at room temperature within a few hours, giving the carbonyl complex **7** as the main product,^[11, 15] complex **4** remains unchanged in benzene solution after 24 hours at room temperature

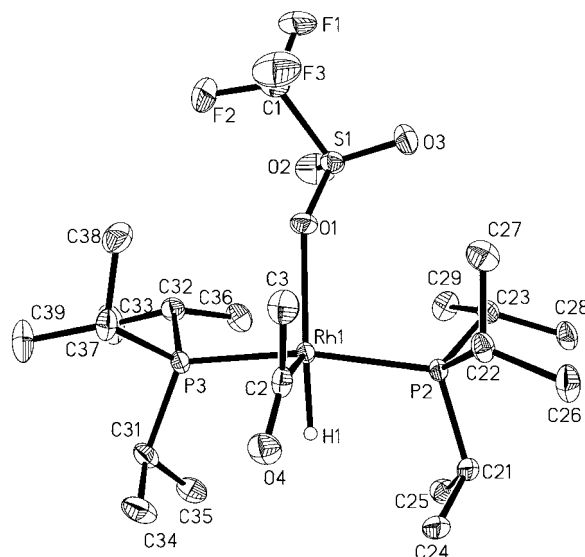


Figure 2. Structure of **4** (ORTEP plot; hydrogen atoms, except H1, are omitted for clarity). Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Rh1-C2 $1.949(2)$, Rh1-O1 $2.2986(15)$, Rh1-P3 $2.3428(7)$, Rh1-P2 $2.3712(7)$, Rh1-H1 $1.46(2)$; C2-Rh1-O1 $103.64(8)$, C2-Rh1-P3 $91.40(6)$, O1-Rh1-P3 $93.31(5)$, C2-Rh1-P2 $94.10(6)$, O1-Rh1-P2 $98.17(5)$, P3-Rh1-P2 $165.73(2)$, C2-Rh1-H1 $87.3(9)$, P2-Rh1-H1 $80.5(9)$, P3-Rh1-H1 $86.6(9)$, O1-Rh1-H1 $169.1(9)$.

(Scheme 1). Thus, unlike other coordinatively unsaturated acylrhodium complexes,^[1b, 11, 15] **4** is surprisingly stable towards decarbonylation. Apparently, since the acyl ligand is located in the apical position (Figure 2), the *cis* coordination site required for decarbonylation is not available.^[16] This result also indicates that the triflate ligand does not readily dissociate from the Rh^{III} complex in benzene. Surprisingly, unlike **1** and **2**, complex **3** does not react with MeCHO or PhCHO under the same conditions, or even after two days with a 100-fold excess of benzaldehyde.

The nucleophilicity of **1** was compared with that of the chloro complexes **2** and **3**, using MeI as an electrophile. The addition of MeI to rhodium(I) complexes is a classical, well-studied reaction of industrial significance, which usually proceeds smoothly and is routinely used as a method for the formation of Rh-C bonds.^[17] As expected, complexes **2** and **3** react smoothly with a stoichiometric amount of MeI in benzene at room temperature to yield the square-pyramidal complex *trans*- $[(\text{iPr}_3\text{P})_2\text{Rh}(\text{Cl})(\text{I})(\text{Me})]$ (**8**) (Me in the apical position) and the octahedral complex *mer*- $[(\text{Et}_3\text{P})_3\text{Rh}(\text{Cl})(\text{I})(\text{Me})]$ (**10**).^[12, 18] The analogous reactions of MeI with $[(\text{Cy}_3\text{P})_2\text{RhCl}]$ (Cy = cyclohexyl) and $[(\text{Me}_3\text{P})_3\text{RhCl}]$ complexes result in $[(\text{Cy}_3\text{P})_2\text{Rh}(\text{Cl})(\text{I})(\text{Me})]$ ^[19a] and $[(\text{Me}_3\text{P})_3\text{Rh}(\text{Cl})(\text{I})(\text{Me})]$,^[19b] respectively. Interestingly, whereas **3** reacts readily with one equivalent of MeI even at -20°C , no significant reaction of **1** with MeI (or with MeOTf) is observed after several hours at room temperature, even when a fivefold excess of MeI is used.

This difference in chemoselectivity is strikingly apparent in competitive experiments in which complexes **1–3** were treated with a 10-fold excess of a 1:1 molar mixture of MeI and RCHO ($\text{R} = \text{Me}$ or Ph) in a solution of C_6D_6 . *trans*- $[(\text{iPr}_3\text{P})_2\text{Rh}(\text{N}_2)\text{Cl}]$ (**11**)^[20] was also examined in the competitive experiments, and the results are presented in Table 1.

Table 1. Competitive reactivity of Rh^I complexes in oxidative addition reactions.

Complex	Substrates ^[a]	Products	Molar ratio of RCHO/MeI adducts ^[c]
1	MeCHO + MeI	MeCHO adduct 4	100:0
	PhCHO + MeI	PhCHO adduct 12 ^[b]	100:0
2	MeCHO + MeI	mixture of 6 , 8 , 9	80:20
	PhCHO + MeI	mixture of 5 , 8 , 9	65:35
11	MeCHO + MeI	mixture of 6 , 7 , 8 , 9	35:65
	PhCHO + MeI	mixture of 5 , 7 , 8 , 9	15:85
3	MeCHO + MeI	mainly 10	0:100
	PhCHO + MeI	mainly 10	0:100

[a] Reaction conditions: room temperature, benzene solution, molar ratio of RCHO/MeI/Rh^I complex = 10:10:1. [b] Complex **12**, [(iPr₃P)₂Rh(OTf)(H)(COPh)], was synthesized analogously to **4**.^[12] [c] The ratio is based on ³¹P and ¹H NMR data. Compounds **7** and **9** are included in the total ratio of the addition products of RCHO and MeI, respectively.

It is apparent that the four similar Rh complexes behave very differently in the oxidative addition of aldehydes and MeI. [(iPr₃P)₂RhOTf] (**1**) reacts selectively with aldehydes, leaving MeI untouched, but [(Et₃P)₃RhCl] (**3**) reacts selectively with MeI, leaving the aldehydes unconverted. Although the reactions of [(iPr₃P)₂RhCl]₂ (**2**) and *trans*-[(iPr₃P)₂Rh(N₂)Cl] (**11**) under the same conditions are not selective, they exhibit opposite relative reactivity towards aldehydes and MeI.

Further studies are required to determine the reasons for the differences in reactivity and selectivity of the phosphane-rhodium(II) complexes; however, a possible explanation is that the oxidative addition of aldehydes requires a three-coordinate, 14-electron Rh^I complex, whereas the oxidative addition of MeI proceeds via the four-coordinate, 16-electron complex. The oxidative addition of aldehydes to [(Me₃P)₃RhCl] was shown to involve the 14-electron complex,^[8] as were other C–H oxidative addition reactions to L₃RhCl, which proceed via a three-centered transition state.^[21] On the other hand, MeI reacts with L₃RhCl by means of an S_N2-type mechanism, in which the four-coordinate complex is the active species.^[17–f, 17i, 22]

The lack of reactivity of **3**, and the lower reactivity of **11** with aldehydes than of **1** and **2**, may be due to the ability of **1** and **2** to easily generate the three-coordinate species in solution,^[23] whereas phosphane dissociation from **3** and **11** may be more difficult.^[24, 25] On the other hand, **3** reacts with MeI even at low temperatures, since the generation of the three-coordinate species is probably not required. Apparently, electron density at the metal center plays a key role in the addition of MeI.^[26] Compound **2** is more reactive than **1**, probably due to the chloride ligand being a better donor than the triflate. Interestingly, the dimer **2** reacts preferentially with aldehydes, whereas the monomer **11** reacts preferentially with MeI. This result is in agreement with the greater ease of formation of a three-coordinate complex with **2**.^[23a, 27]

This study demonstrates unprecedented ligand-controlled selectivity of similar rhodium(II) complexes in classical oxidative addition reactions. The reactivity of complexes of the type [P_nRhX] is strongly dependent on the number and nature of the alkylphosphane (P) and the halide or triflate (X), and can be selectively directed to the oxidative addition of an

aldehyde or MeI. The observed selectivity may be potentially useful in reactions where substrates containing formyl groups (and perhaps other groups with reactive nonpolar bonds) and electrophilic centers in the same system are involved. An example of high substrate selectivity in such mixtures is described herein.

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- (dt, $^3J(\text{P,H}) = 13.6 \text{ Hz}$, $^3J(\text{H,H}) = 7.5 \text{ Hz}$, 9H; $\text{ClRhP}(\text{CH}_2\text{CH}_3)_3$; $^{13}\text{C}\{^1\text{H}\}$ NMR: $\delta = 0.11$ (ddt, $^1J(\text{Rh,C}) = 21.2 \text{ Hz}$, $^2J(\text{P}(\text{unique}),\text{C}) = 8.2 \text{ Hz}$, $^2J(\text{P}(\text{mutually trans}),\text{C}) = 5.5 \text{ Hz}$, RhCH_3). **12**: $^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta = 45.8$ (d, $^1J(\text{Rh,P}) = 123 \text{ Hz}$, 2P); ^1H NMR: $\delta = 8.09$ (m, 2H; COPh), 7.05 (m, 3H; COPh), 2.23 (m, 6H; $\text{PCH}(\text{CH}_3)_2$), 1.06 (dvt, $J = 6.9 \text{ Hz}$, 18H; $\text{PCH}(\text{CH}_3)_2$), 0.99 (dvt, $J = 7.0 \text{ Hz}$, 18H; $\text{PCH}(\text{CH}_3)_2$), -20.92 (dt, $^2J(\text{Rh,H}) = 44.5 \text{ Hz}$, $^3J(\text{P,H}) = 10 \text{ Hz}$, 1H; RhH); IR (film): $\tilde{\nu} = 1650 \text{ cm}^{-1}$ ($\text{C}=\text{O}$).
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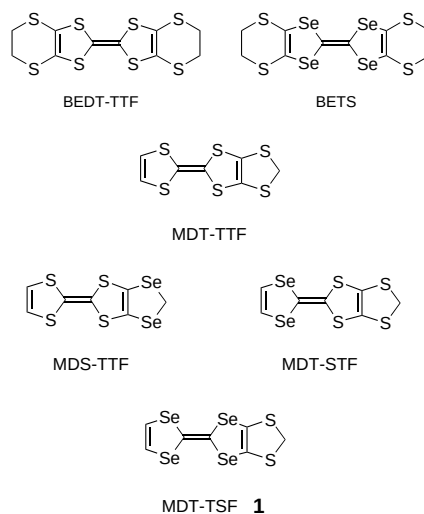
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Quasi One-Dimensional Organic Superconductor MDT-TSF·AuI₂ with $T_c = 4.5 \text{ K}$ at Ambient Pressure**

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Although the first organic superconductors were prepared from radical-cation salts (Bechgaard salts) based on tetrathyltetraselenafulvalene (TMTSF) under extremely cryogenic conditions ($T_c < 1.4 \text{ K}$), higher T_c superconductors were developed from heterocycle-fused tetrathiafulvalenes (TTFs), represented by bis(ethylenedithio)tetrathiafulvalene (BEDT-TTF).^[1] Whereas the Bechgaard salts have quasi one-dimen-



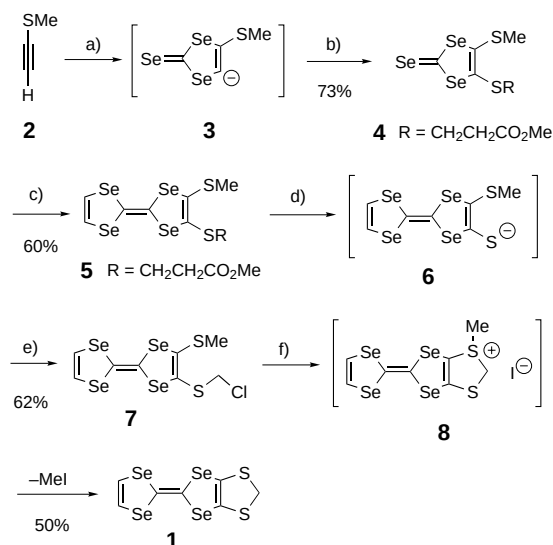
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sional electronic structures, the subsequent superconductors are characterized by unique quasi two-dimensional electronic structures due to multisulfur atomic interactions. The most typical is the κ -type salts, such as (BEDT-TTF)₂[Cu[N(CN)₂]₂X] salts with T_c values higher than 10 K,^[2] which no longer have donor-stacked structures. In this regard, it may be worthy to note that methylenedithiotetrathiafulvalene (MDT-TTF), which does not include as many sulfur atoms as BEDT-TTF, can form a κ -type superconducting AuI₂ salt with a relatively high T_c of 4.1–4.3 K.^[3] Since replacement of some or all sulfur atoms in such multisulfur-based donors by selenium atoms provides novel electron donors with different electronic structures, in particular strengthening its metallic character due to strong nonbonding selenium interactions,^[4] we are interested in the selenium variants of MDT-TTF. From this series, the methylenediseleno-TTF (MDS-TTF)^[5] and methylenedithio-diselenadithiafulvalene (MDT-STF)^[6] have been already synthesized but no superconducting salts from them have been so far reported. The discovery of novel λ -type superconductors with a high T_c (9.7 K) based on bis(ethylenedithio)tetraselenafulvalene (BETS) as a selenium variant of BEDT-TTF^[7] suggests the most intriguing selenium variant of MDT-TTF might be methylenedithiotetraselenafulvalene (MDT-TSF, **1**), which still remains unknown apparently due to the lack of an appropriate synthetic method. We now would like to present the efficient synthesis of **1** and the superconducting behavior of its AuI₂ salt.

For the synthesis of **1**, we have adopted a synthetic strategy of the initial formation of the TSF skeleton followed by the construction of the outer 1,3-dithiole ring, as shown in Scheme 1. This route involves a combination of very effective synthetic techniques recently developed by our group, namely, one-pot formation of 1,3-diselenole-2-selone from a terminal alkyne,^[8] a trialkyl phosphite-mediated coupling reaction to the TSF derivative, and finally heterocycle formation by transalkylation on a chalcogen atom.^[9] In addition, we have taken advantage of a deprotection/realkylation protocol of a novel, protected TSF–thiolate building



Scheme 1. Synthesis of MDT-TSF (**1**). a) BuLi, Se, CSe₂, THF; b) NCS(CH₂)₂CO₂Me; c) 1,3-diselenole-2-selone, P(OMe)₃, C₆H₆; d) CsOH·H₂O; e) ClCH₂I; f) NaI, 2-butanone.

block **5**.^[10] For the first step, methylthioacetylene (**2**)^[11] was successively treated with *n*BuLi, selenium powder, and carbon diselenide, to generate in situ the vinyl anion intermediate (**3**), which was then quenched with 3-thiocyanatopropionic acid methyl ester^[12] to give a 1,3-diselenole-2-selone derivative (**4**) in 73% yield. Cross-coupling of **4** with unsubstituted 1,3-diselenole-2-selone gave the desired asymmetrical TSF derivative **5** in 60% yield. Treatment of **5** with cesium hydroxide monohydrate in DMF generated the reactive TSF monothiolate (**6**), which was alkylated in situ with chloriodomethane to give **7** in 62% yield. Formation of the outer 1,3-dithiolen ring was achieved by an initial halogen exchange to the corresponding iodide followed by spontaneous transalkylation into **1** via the sulfonium salt **8**.

Orange platelike crystals of **1** were obtained by recrystallization from chlorobenzene and subjected to an X-ray crystallographic analysis. The molecule has a slightly bent structure and forms a face-to-face dimer with a center of symmetry arranged orthogonally to the neighboring dimers. Cyclic voltammetry of **1** showed two reversible redox waves at 0.52 and 0.75 V versus a Ag/AgCl reference electrode in benzonitrile. Both the first and second half-wave oxidation potentials are nearly the same as those of the parent TSF ($E_{1/2}$ = 0.49 and 0.78 V).

Electrocrystallization of **1** in chlorobenzene containing tetrabutylammonium diiodoaurate as a supporting electrolyte gave needle-shaped crystals in a few days. Its electrical conductivity is very high (2000 S cm⁻¹, an average of 8 samples) at room temperature. Resistivity as a function of temperature monotonously decreases down to low temperature and abruptly drops at 4.5 K, which is characteristic of the onset of a superconducting transition (Figure 1). Magnetic

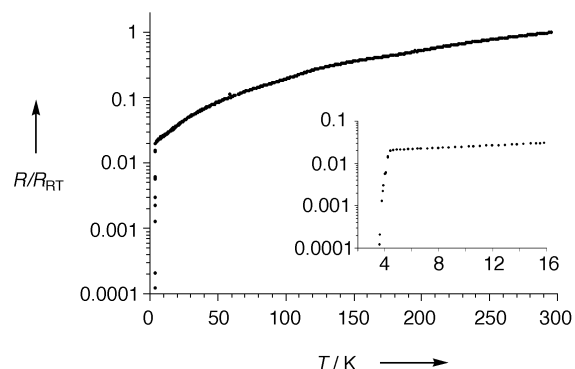


Figure 1. Temperature dependence of conductivity of **1**₂·AuI₂. Inset: the domain 2–16 K, expanded.

susceptibility with a SQUID susceptometer also reveals its superconductivity (Figure 2). The diamagnetic shielding at 2 K shows 80% of the perfect diamagnetism, to indicate that the salt is a bulk superconductor. In both zero-field cooled (ZFC) and field cooled (FC) measurements, the susceptibility starts to decrease at 4.2 K, which is slightly lower than that of the conductivity measurement.

An X-ray crystal structure analysis revealed an interesting structural feature of the salt:^[13] The MDT-TSF donor, unlike the neutral one, is completely planar and uniformly stacked

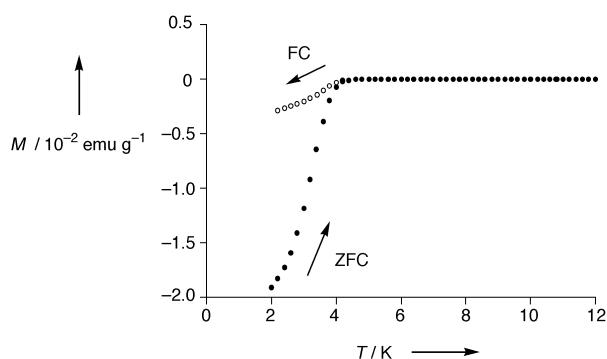


Figure 2. Temperature dependence of the magnetic susceptibility of $1_2 \cdot \text{AuI}_2$.

along the a -axis (Figure 3a). In the anion layer, the position and population of AuI_2^- units are not precisely determined, presumably due to the disorder or different periodicity of the anions from the donor arrangement. The ratio of the donor to

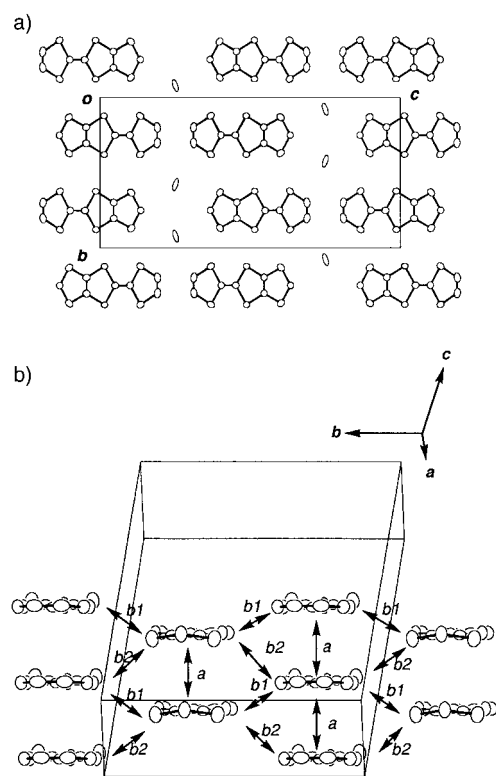


Figure 3. a) Crystal structure of $1_2 \cdot \text{AuI}_2$ viewed along a -axis direction and b) a side view of the donor sheet. Calculated overlap integrals are $a = -18.89 \times 10^{-3}$, $b1 = 3.64 \times 10^{-3}$, and $b2 = 0.4 \times 10^{-3}$.

anion is determined as approximately 2:1 on the basis of an elemental analysis.^[14] In the donor sheets, there are many nonbonded Se–Se contacts, not only in the intrastacking direction but also interstacking direction (Figure 3b). These nonbonded Se–Se interactions are presumably responsible for its unexpected stacking structure that is quite different from the κ -type of the related superconducting $(\text{MDT-TTF})_2 \cdot \text{AuI}_2$ salt. A calculation using the extended-Hückel tight-binding approximation^[15] indicated that the overlap integrals between intrastacks are about five times as large as that

between the interstacks. This means that the $(\text{MDT-TSF})_2 \cdot \text{AuI}_2$ salt is essentially a quasi one-dimensional superconductor, which is reminiscent of the Bechgaard salts.^[1]

In summary, we have succeeded in the synthesis of a new electron donor MDT-TSF and its superconducting radical cation salt $(\text{MDT-TSF})_2 \cdot \text{AuI}_2$. Unexpectedly, the salt, in spite of relatively high T_c , has a quasi one-dimensional stacking structure. In addition, it is noteworthy that the room temperature conductivity of $(\text{MDT-TSF})_2 \cdot \text{AuI}_2$ is extraordinary high (2000 Scm^{-1}) among organic superconductors. These results clearly demonstrate the unique electronic structure of MDT-TSF, which allows enhanced nonbonded Se–Se interactions.

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- [13] X-ray crystal structure analyses were made on a Rigaku AFC7R four-circle diffractometer (MoK_α radiation $\lambda = 0.71069 \text{ \AA}$, graphite monochromator, $T = 296 \text{ K}$, $\omega - 2\theta$ scan, $2\theta_{\text{max}} = 55.0^\circ$). The structure for $1_2 \cdot \text{AuI}_2$ was solved with a direct method and refined by a full-matrix least-squares fit on $|F|$. All calculations were performed using the crystallographic software package teXsan (Molecular Structure Corporation, **1985**, **1992**). Crystal data for $1_2 \cdot \text{AuI}_2$: $\text{C}_{14}\text{H}_8\text{S}_2\text{Se}_2\text{AuI}_2$, $M = 1386.91$, black needles ($0.65 \times 0.03 \times 0.02 \text{ mm}$), orthorhombic, space group $Pnma$ (No. 62), $a = 4.016(6)$, $b = 12.513(3)$, $c = 25.424(3) \text{ \AA}$, $V = 1277(1) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 3.605 \text{ g cm}^{-3}$, $\mu = 199.27 \text{ cm}^{-1}$, $R = 0.039$,

$wR = 0.051$, 1534 measured reflections, 946 observed reflections ($I > 3.0\sigma(I)$), 83 refined parameters. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-146823. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Synthesis of $[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$ $n = 8–10$: Metal Boride Particles That Stretch the Cluster Structure Paradigms**

Sundargopal Ghosh, Maoyu Shang, Yaping Li, and Thomas P. Fehlner*

Metal borides are substances of considerable interest because of their physical, chemical, and electrical properties.^[1–4] Their simple stoichiometries belie complex extended structures and consequently, metal borides are rarely treated in basic inorganic texts. Yet, it was from metal borides that a solution to the molecular borane cluster structure problem arose, for example, CaB_6 formulated as a Zintl phase $[\text{Ca}^{2+}][\text{B}_6^{2-}]$ with a three-dimensional network of octahedral B_6 cages^[5] comparable with discrete $[\text{B}_6\text{H}_6^{2-}]$ ions.^[6] At the other end of the compositional scale, metal clusters with interstitial boron atoms have been identified which have the local bonding environment of boron in metal-rich borides.^[7] However, the borides of intermediate compositions, for example, CrB_4 ^[8], find no models in the molecular world. To date there has been no need to invoke a comparison as nearly all known metallaboranes contain late transition metal fragments and follow the same structural paradigm as the boranes.^[9, 10] Indeed it is a measure of the success of the cluster-electron counting rules and the isolobal analogy that boranes, metallaboranes, and metal clusters are linked in such a simple, conceptually pleasing, fashion.^[11–14]

Recently we discovered a few unusual compounds that do not fit the mold of the borane paradigm.^[15] Compared with

compounds containing later transition metal fragments, these compounds exhibit structures characterized by high metal-coordination number, cross-cluster bonds, and unexpected stability for low valent Group 6 and 7 metal compounds. In trying to understand the cause of this behavior we adopted an approach which has been usefully applied to borides of intermediate stoichiometries.^[16] Burdett and co-workers have pointed out that information on electronic structure is revealed by the change in structure with metal type at constant stoichiometry.^[17, 18] Specifically, for MB_2 and MB_4 borides (where $\text{M} = \text{metal}$) they demonstrated a correlation between the occupation of orbitals of MM and MB antibonding character and observed structure variation. In going from late to early transition metals, the metal-atom coordination number increases and the extent of MM and MB bonding increases. For $[(\text{Cp}^*\text{WH})_2\text{B}_7\text{H}_7]$, $[(\text{Cp}^*\text{Re})_2\text{B}_7\text{H}_7]$, and $[(\text{Cp}^*\text{W})_3\text{HB}_8\text{H}_8]$, we argued that in moving from late to earlier transition metals the geometric deviations from the cluster shapes of borane chemistry reflect a similar transition from electronic structures characteristic of boranes to those characteristic of borides.

An unconventional view based on three compounds constitutes an interesting curiosity rather than a useful idea. In further support we can now offer the characterization of a homologous series of metallaboranes that begins with $[(\text{Cp}^*\text{Re})_2\text{B}_7\text{H}_7]$. These compounds establish a new set of cluster geometries remarkably different from the canonical deltahedra of the $[\text{B}_n\text{H}_n]^{2-}$ boranes that underpin the cluster-electron counting rules.^[19, 20] The oblate cluster shapes, high metal-coordination numbers, and cross-cluster bonds featured support the idea that variation in the transition metal can drive a change from borane- to boride-like bonding.

Subsequent to the isolation of $[(\text{Cp}^*\text{Re})_2\text{B}_7\text{H}_7]$ from the reaction of $[\text{Cp}^*\text{ReCl}_4]$ and monoboranes,^[15] we found that it is formed in a more straightforward manner from the reaction of $[(\text{Cp}^*\text{ReH}_2)_2\text{B}_4\text{H}_4]$ with BH_3THF .^[21] Further development of this reaction permits the compounds $[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$, $n = 8–10$, to be isolated and characterized. Although produced in a mixture, they are insensitive to air and moisture and can be separated by thin layer chromatography (TLC) on the laboratory bench. Reactions of pure $[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$, $n = 7–10$, with BH_3THF demonstrate sequential cluster build up. So far all efforts to produce a compound with $n > 10$ have failed.

The molecular structures of the new compounds in the solid state,^[22] are shown in Figures 1–3. $[(\text{Cp}^*\text{Re})_2\text{B}_8\text{H}_8]$ possesses a C_2 axis bisecting the B1-B2 and B5-B6 edges (See also Figure 4). Three ^{11}B resonances in the intensity ratio 2:4:2 are observed by solution NMR spectroscopy in the temperature range -90 to 22°C suggesting accidental overlap of two signals or a low-barrier fluxional process in solution. The complex $[(\text{Cp}^*\text{Re})_2\text{B}_9\text{H}_9]$ possesses a plane of symmetry passing through the Re atoms and B5 consistent with the ^{11}B resonances (2:2:2:1) in solution NMR spectroscopy. The complex $[(\text{Cp}^*\text{Re})_2\text{B}_{10}\text{H}_{10}]$ possesses a C_2 axis bisecting the B2-B3 and B7-B8 edges consistent with the observed ^{11}B resonances (2:2:2:2:2). The wide range of boron chemical shifts and some uncharacteristically upfield terminal BH resonance signals constitutes the NMR signature of this

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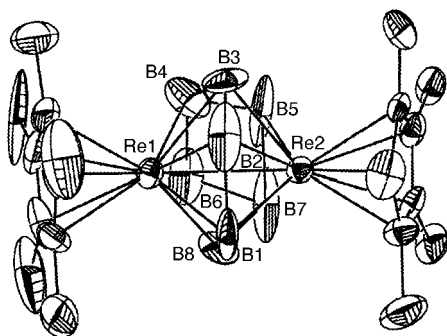


Figure 1. Molecular structure of $[(\text{Cp}^*\text{Re})_2\text{B}_8\text{H}_8]$. Selected distances [$\text{\AA}$]: Re1-B2 2.04(3), Re1-B1 2.09(3), Re1-B8 2.16(2), Re1-B4 2.211(19), Re1-B3 2.27(3), Re1-B6 2.33(3), Re1-Re2 2.8345(8), Re2-B2 2.05(2), Re2-B1 2.076(18), Re2-B7 2.19(2), Re2-B3 2.21(2), Re2-B5 2.31(2), Re2-B8 2.35(3), B1-B2 1.82(5), B1-B8 1.94(5), B2-B3 1.65(4), B3-B4 1.76(5), B3-B5 2.18(5), B4-B5 1.55(3), B4-B6 1.74(4), B5-B7 1.89(5), B5-B6 2.03(5), B6-B7 1.73(4), B6-B8 2.02(5), B7-B8 1.66(5).

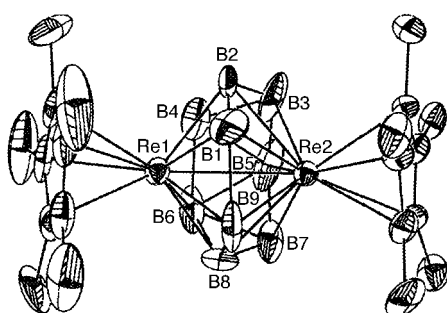


Figure 2. Molecular structure of $[(\text{Cp}^*\text{Re})_2\text{B}_9\text{H}_9]$. Selected distances [$\text{\AA}$]: Re1-B1 1.982(14), Re1-B9 2.075(12), Re1-B8 2.187(14), Re1-B6 2.209(12), Re1-B4 2.212(14), Re1-B2 2.216(15), Re1-Re2 2.8604(5), Re2-B9 2.165(11), Re2-B1 2.198(11), Re2-B3 2.215(13), Re2-B7 2.217(14), Re2-B5 2.299(16), Re2-B2 2.336(11), Re2-B8 2.402(13), B1-B2 1.70(2), B1-B9 1.869(18), B2-B3 1.70(2), B2-B4 1.83(3), B3-B5 1.55(2), B3-B4 1.63(2), B4-B6 1.86(2), B4-B5 1.858(18), B5-B7 1.67(2), B5-B6 1.86(2), B6-B7 1.736(19), B6-B8 1.82(2), B7-B8 1.646(19), B8-B9 1.794(17).

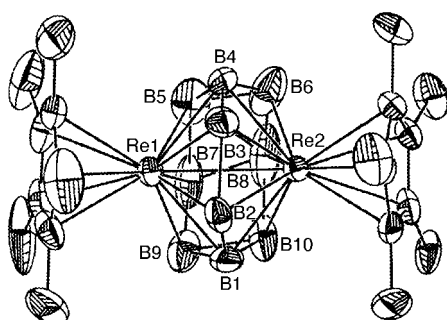


Figure 3. Molecular structure of $[(\text{Cp}^*\text{Re})_2\text{B}_{10}\text{H}_{10}]$. Selected distances [$\text{\AA}$]: Re1-B2 2.120(14), Re1-B3 2.185(15), Re1-B4 2.248(14), Re1-B9 2.268(17), Re1-B1 2.271(18), Re1-B5 2.272(17), Re1-B7 2.408(18), Re2-B3 2.131(13), Re2-B6 2.18(2), Re2-B2 2.190(13), Re2-B4 2.226(15), Re2-B1 2.226(14), Re2-B8 2.31(2), B1-B2 1.67(2), B1-B9 1.72(3), B1-B10 1.83(3), B2-B3 1.747(19), B3-B4 1.67(3), B4-B6 1.58(3), B4-B5 1.74(3), B5-B6 1.59(3), B5-B7 1.78(3), B5-B8 1.93(3), B6-B8 1.52(4), B7-B9 1.65(3), B7-B8 1.67(3), B7-B10 2.02(3), B8-B10 1.79(4), B9-B10 1.62(2).

structure type. The Re atoms occupy two vertices of connectivity 6 in $[(\text{Cp}^*\text{Re})_2\text{B}_8\text{H}_8]$, one vertex of connectivity 6 and one of connectivity 7 in $[(\text{Cp}^*\text{Re})_2\text{B}_9\text{H}_9]$, and two of connectivity 7 in $[(\text{Cp}^*\text{Re})_2\text{B}_{10}\text{H}_{10}]$. Each compound also

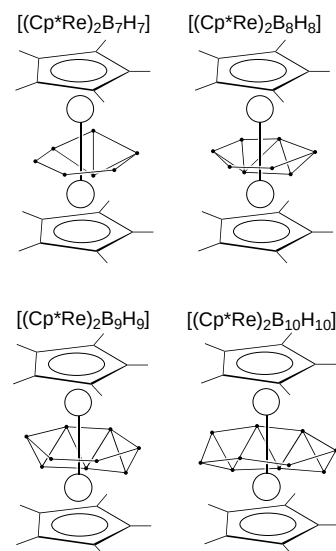


Figure 4. Structural representation of $[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$, $n = 7-10$, with heteronuclear bonding deleted. Open circles = Re, closed circles = BH.

contains a cross-cluster Re-Re bond ($d_{\text{Re-Re}}$ lies between 2.82 and 2.86 $\text{\AA}$).

As the Cp^*Re fragment is formally a 0-electron contributor to cluster bonding each of these clusters has $p-2$ sep (skeletal electron pairs) rather than the $p+1$ sep required for a normal deltahedral *closo* borane with p vertices, for example $[(\text{CpNi})_2\text{B}_n\text{H}_n]$, $n = 8, 10$ ($\text{Cp} = \text{C}_5\text{H}_5$).^[23, 24] Neither the capping nor cluster-fusion principles account for the structures of these hypoelectronic metallaboranes.^[14] Diamond-square-diamond (dsd) rearrangements (illustrated for $[(\text{Cp}^*\text{Re})_2\text{B}_8\text{H}_8]$, in Figure 5) convert the canonical geometries into those observed for $[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$, $n = 7-10$. In such a rearrangement the number of bonded edges remains constant but vertices of higher connectivity are generated, for example, for $n = 8$ (bicapped square antiprism) four vertices of connectivity 5 are converted into two vertices of connectivity 6 and two of connectivity 4 in the observed structure. As a necessary consequence, the spherical canonical cluster becomes oblate with a relatively short cross-cluster distance between the high-coordinate vertices. The metal atoms occupy these vertices and the short cross-cluster distance permits the formation of an Re-Re bond. In

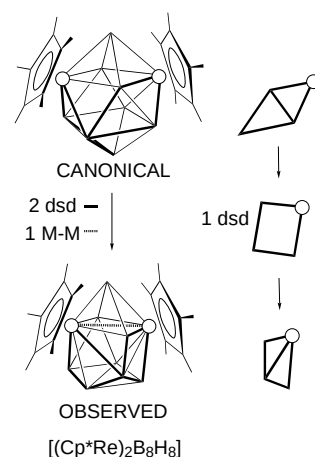


Figure 5. Generation of the observed structure of $[(\text{Cp}^*\text{Re})_2\text{B}_8\text{H}_8]$ from a bicapped square-antiprismatic cluster by two diamond-square-diamond (dsd) rearrangements (bold lines). The Re-Re bond is indicated by the dashed line and one dsd rearrangement is shown on the right.

for example, the pentagonal antiprism of the borane fragment of $[(\text{Cp}^*\text{Re})_2\text{B}_{10}\text{H}_{10}]$ in the canonical icosahedral form has become partially unraveled in the observed structure (Figure 6). Considering the robust nature of icosahedral boranes and carboranes, the dominance of transition metal bonding over main group bonding in these boron-rich compounds is surprising.

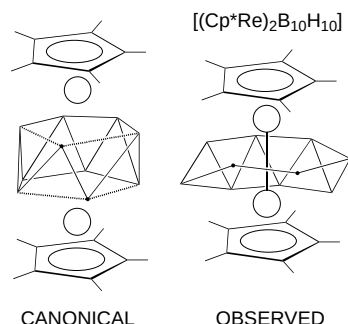


Figure 6. Loss of B–B bonding in the conversion of an icosahedral cluster shape into that observed for $[(\text{Cp}^*\text{Re})_2\text{B}_{10}\text{H}_{10}]$; lost bonds are shown by the dashed lines.

The compound $[(\text{Cp}^*\text{Re})_2\text{B}_6\text{H}_6]$ can be considered the parent member of the $[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$ series. Although this compound is unknown, the isolobal compounds $[(\text{Cp}^*\text{Re})_2\{\mu\text{-}\eta^6\text{-}\eta^6\text{-B}_4\text{H}_4\text{Co}_2(\text{CO})_5\}]^{[25]}$ and $[(\text{Cp}^*\text{Cr})_2\{\mu\text{-}\eta^6\text{-}\eta^6\text{-C}_3\text{H}_6\text{C}_2\text{B}_4\text{H}_4\}]^{[26]}$ with cross-cluster M–M bonds have been characterized. These compounds are triple-decker complexes^[27] and they provide insight on the electronic origin of the shapes observed. Comparing 9 sep $[(\text{Cp}^*\text{Rh})_2\{\mu\text{-}\eta^6\text{-}\eta^6\text{-C}_4\text{H}_4\text{B}_2\text{Me}_2\}]^{2+}$ ^[28] with 6 sep $[(\text{Cp}^*\text{Re})_2\{\mu\text{-}\eta^6\text{-}\eta^6\text{-B}_6\text{H}_6\}]$ shows that as the Cp^*M fragments are moved within bonding distance three orbitals, which are filled in the 9 sep compound, are emptied and a substantial HOMO–LUMO gap is produced for 6 sep.^[29] Likewise, the generation of the observed structure of $[(\text{Cp}^*\text{Re})_2\text{B}_7\text{H}_7]$ from the canonical tricapped trigonal prismatic geometry causes three orbitals to rise sufficiently high in energy to become unoccupied.^[15, 30] As with the triple-decker complexes, these molecular orbitals consist of an ReRe antibonding orbital and two ReB orbitals that are boron–ring–metal δ antibonding. The ring orbitals emptied are also BB bonding which is consistent with decreased B–B bonding. In essence, the low electron count of the metal center demands additional bonding which is satisfied by a nonspherical shape at the expense of some B–B bonding. Like the metal borides of intermediate composition, an earlier transition metal fragment creates electronic requirements that are expressed in structural features not previously observed for boranes or metallaboranes containing later transition metal fragments.

Experimental Section

$[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$: $\text{BH}_3 \cdot \text{THF}$ (8-fold excess) was slowly added to a 100 mL Schlenk tube containing $[(\text{Cp}^*\text{ReH}_2)_2\text{B}_4\text{H}_4]$ (0.15 g, 0.21 mmol) in toluene (15 mL). The mixture was heated for 26 h at 90 °C, volatiles were removed in vacuo, the residue extracted in hexane: CH_2Cl_2 (9:1 v/v), and filtered through Celite. After removal of solvent from the filtrate, the residue was subjected to chromatographic work-up using silica gel TLC plates. Elution

with hexane: CH_2Cl_2 (8:2 v/v) yielded four closely spaced bands: yellow, $R_f = 0.23$, $[(\text{Cp}^*\text{Re})_2\text{B}_7\text{H}_7]$ (0.02 g, 17%); orange-red, $R_f = 0.14$, $[(\text{Cp}^*\text{Re})_2\text{B}_8\text{H}_8]$ (0.05 g, 38%); red, $R_f = 0.09$, $[(\text{Cp}^*\text{Re})_2\text{B}_9\text{H}_9]$ (0.01 g, 10%); yellow, $R_f = 0.05$, $[(\text{Cp}^*\text{Re})_2\text{B}_{10}\text{H}_{10}]$ (0.01 g, 7%). X-ray quality crystals were grown by slow diffusion of a hexane: CH_2Cl_2 (9:1 v/v) solution of $[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$ ($n = 8-10$) at 5 °C. Selected data for $[(\text{Cp}^*\text{Re})_2\text{B}_n\text{H}_n]$, $n = 8$: MS (EI): $[M^+]$ (max) = 736 (isotopic pattern for 2 Re and 8 B atoms), $^{12}\text{C}_{20}\text{H}_{38}\text{B}_8^{187}\text{Re}_2$, calcd: 739.2755; found: 739.2722 (exact mass measurement on $[M^+ - 1]$); ^{11}B NMR (C_6D_6 , 22 °C, 96 MHz): $\delta = 97.92$ (d, $^1J(\text{B},\text{H}) = 163$ Hz, 2B), 65.76 (d, $^1J(\text{B},\text{H}) = 136$ Hz, 4B), 21.92 (d, $^1J(\text{B},\text{H}) = 141$ Hz, 2B); ^1H NMR (C_6D_6 , 22 °C, 300 MHz): $\delta = 9.86$ (partially collapsed quartet (pcq), 2BHz ($t = \text{terminal}$)), 9.02 (pcq, 4BHz), 1.86 (s, 30H, 2Cp*), 0.32 (pcq, 2BHz); IR (CH_2Cl_2 , cm^{-1}): 2521 w, 2443 w (B–Hr). $n = 9$: MS (EI): $[M^+]$ (max) = 748 (isotopic pattern for 2 Re and 9 B atoms) $^{12}\text{C}_{20}\text{H}_{39}\text{B}_9^{187}\text{Re}_2$, calcd: 751.2926; found: 751.2908 (exact mass measurement on $[M^+ - 1]$); ^{11}B NMR (C_6D_6 , 22 °C): $\delta = 94.08$ (d, $^1J(\text{B},\text{H}) = 168$ Hz, 2B), 76.19 (d, $^1J(\text{B},\text{H}) = 153$ Hz, 2B), 35.49 (d, $^1J(\text{B},\text{H}) = 129$ Hz, 2B), 1.09 (d, $^1J(\text{B},\text{H}) = 130$ Hz, 2B), –28.73 (d, $^1J(\text{B},\text{H}) = 130$ Hz, 1B); ^1H NMR (C_6D_6 , 22 °C): $\delta = 11.21$ (pcq, 2BHz), 10.23 (pcq, 2BHz), 8.46 (pcq, 2BHz), 1.92 (s, 15H, 1Cp*), 1.51 (s, 15H, 1Cp*), –0.12 (pcq, 2BHz), –2.26 (pcq, 1BHz); IR (CH_2Cl_2 , cm^{-1}): $\tilde{\nu} = 2532$ w, 2430 w (B–Hr). $n = 10$: MS (EI): $[M^+]$ (max) = 760 (isotopic pattern for 2 Re and 10 B atoms) $^{12}\text{C}_{20}\text{H}_{40}\text{B}_{10}^{187}\text{Re}_2$, calcd: 763.3098; found: 763.3126 (exact mass measurement on $[M^+ - 1]$); ^{11}B NMR (C_6D_6 , 22 °C): $\delta = 59.95$ (d, $^1J(\text{B},\text{H}) = 175$ Hz, 2B), 50.39 (d, $^1J(\text{B},\text{H}) = 158$ Hz, 2B), 16.14 (d, $^1J(\text{B},\text{H}) = 135$ Hz, 2B), –10.77 (d, $^1J(\text{B},\text{H}) = 144$ Hz, 2B), –22.91 (d, $^1J(\text{B},\text{H}) = 132$ Hz, 1B); ^1H NMR (C_6D_6 , 22 °C): $\delta = 8.56$ (pcq, 2BHz), 6.84 (pcq, 2BHz), 5.96 (pcq, 2BHz), 1.43 (s, 30H, 2Cp*), 0.28 (pcq, 2BHz), –1.75 (pcq, 2BHz); IR (CH_2Cl_2 , cm^{-1}): $\tilde{\nu} = 2531$ w, 2451 w (B–Hr).

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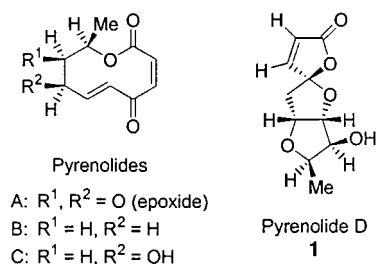
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Total Synthesis of (+)-Pyrenolide D**

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Mauricio Navarro-Villalobos, and David Y. Gin*

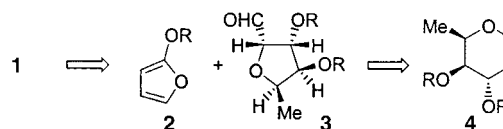
The phylogenetic fungus *Pyrenophora teres* has been a source of a number of fungal metabolites of interesting and varying biological activities. These metabolites include the pyrenolides A–C,^[1] simple macrocyclic lactones that exhibit potent



growth-inhibitory and morphogenic activities toward fungi. A fourth metabolite, pyrenolide D (**1**),^[2] is structurally distinct from the other members of this family in that it incorporates a highly oxygenated tricyclic spiro- γ -lactone structure related to certain members of the cephalosporolide class of natural products.^[3] Moreover, pyrenolide D is further distinguished from the other pyrenolides in that it is not active toward fungi, but rather that it exhibits significant cytotoxic activity toward HL-60 cells. This biological profile, in combination with its densely functionalized polycyclic structure, spawned our efforts to develop a synthetic approach to **1** that would also establish the absolute configuration of the natural product. We report herein the first total synthesis of **1** by a very short sequence. In this context, a method for the efficient con-

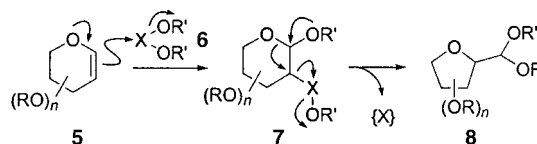
struction of highly oxygenated tetrahydrofurans from glycol starting materials is reported.

Initial retrosynthetic disconnection of **1** (Scheme 1) leads back to a 2-alkoxyfuran **2** and the highly oxygenated tetrahydrofurfural derivative **3** as viable synthetic precursors.



Scheme 1. Retrosynthetic analysis.

Although a number of synthetic strategies to prepare **3** can be envisioned through the synthesis and cyclization of acyclic polyol precursors, we reasoned that a more efficient approach might arise from a stereoselective oxidative ring contraction of a glycol substrate such as 6-deoxy-D-gulal (**4**), incorporating three of the four stereocenters within **3**. For such an oxidative ring contraction process to be feasible, an appropriate electrophilic oxidant **6** (Scheme 2) is required. Not only must



Scheme 2. Oxidative ring contraction of glycols.

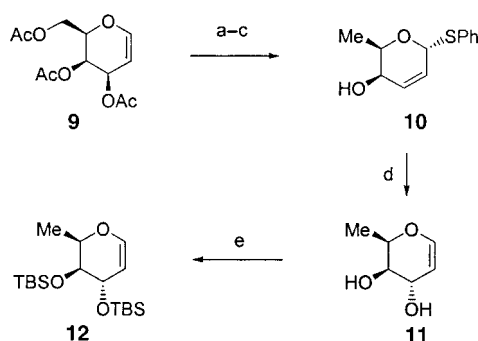
this reagent efficiently perform an electrophilic activation of the glycol substrate (**5**→**7**), but it must also concomitantly install a potent leaving group at the C2 position of the activated pyranoside intermediate **7**. This would hopefully allow 1,2-migration of the endocyclic C–O bond in a displacement of the C2 leaving group, resulting in a net oxidative ring contraction of the glycol substrate to form the C-furanoside product **8**, an intermediate that directly maps onto the proposed synthetic intermediate **3** (Scheme 1). Given our interest in glycol activation processes,^[4] we sought to establish the means to effect the conversion of **5** into **8** as one of the key steps in the synthesis of **1**.

Based on this strategy, the initial synthetic target involved the preparation of 2,3-di-*O*-protected-6-deoxy-D-gulal (**4**) as the desired substrate for the formation of the C-furanoside **3**. The synthesis commenced (Scheme 3) with the preparation of the pseudoglycol **10** from commercially available tri-*O*-acetyl-D-galactal (**9**) through a three-step sequence that included: SnCl₄-catalyzed Ferrier-type glycosylation of thiophenol (84%), acetate hydrolysis and selective tosylation of the C6-hydroxy group (78%), and hydride displacement of the C6-sulfonate functionality (86%).^[5] Subsequent oxidation of the allylic sulfide in **10** with *m*-chloroperoxybenzoic acid led to the formation of the corresponding anomeric sulfoxide, which underwent an Evans–Mislow [2,3]-sigmatropic rearrangement. Subsequent aminolysis of the sulfonate functionality installed the α -C3-OH group (89%).^[6] The resulting 6-deoxy-D-gulal diol **11** was protected as the bis(*tert*-butyldimethylsil-

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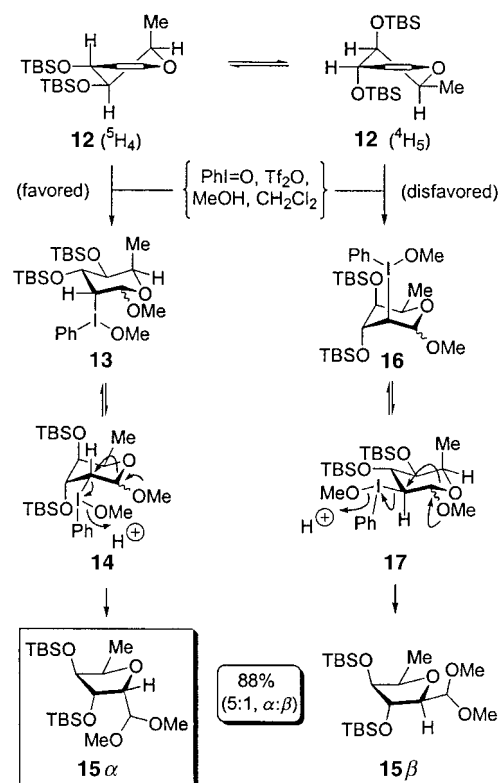


Scheme 3. a) PhSH, SnCl₄ (cat.), CH₂Cl₂, -10 °C, 84%; b) NaOMe, MeOH, 23 °C; Bu₂SnO, MeOH, reflux; *p*-toluenesulfonyl chloride, Bu₄NBr, CHCl₃, 78%; c) LiAlH₄, THF, reflux, 86%; d) *m*-CPBA, CH₂Cl₂, -40 °C; Et₃NH, THF, 23 °C, 89%; e) *tert*-butyldimethylsilyl trifluoromethane sulfonate, 2,4,6-(*tert*-butylpyridine, DMF, 23 °C, 76%; TBS = *tert*-butyldimethylsilyl.

yl) ether to afford **12** (76%), the desired glycal precursor for stereoselective oxidative ring contraction.

Reports on the direct oxidative ring contraction of glycals have been scarce,^[7] with only a few examples of this process proceeding efficiently with stoichiometric quantities of Tl(NO₃)₃ as the oxidant. To avoid the use of highly toxic heavy metal salt oxidants, we focused on the use of hypervalent iodine reagents^[8] (i.e., Scheme 2, **6**, X = PhI) to execute this transformation. Studies involving the reaction of hypervalent iodine reagents with glycal substrates have also been limited, except for the pioneering work of Kirschning who employed various I^{III} reagents to effect efficient allylic 3-*O*-oxidations of protected glycals.^[9] In their allylic oxidation studies, a few examples were reported in which the action of the Koser reagent (PhI(OH)(OTs)) on a glycal substrate led not only to allylic oxidation, but also to the formation of small quantities of tetrahydrofuran by-products ($\leq 35\%$).^[10] Thus, the key challenges in employing I^{III} reagents for glycal oxidative ring contraction in the context of the synthesis of **1** include: 1) the development of a reagent combination that would favor the ring contraction of **12** over the reaction manifold involving C3 oxidation, and 2) the generation of the corresponding C-furanoside **3**, in which the resulting C1-acetal functionality is *cis* to the C3-*O*-substituent, with high stereoselectivity.

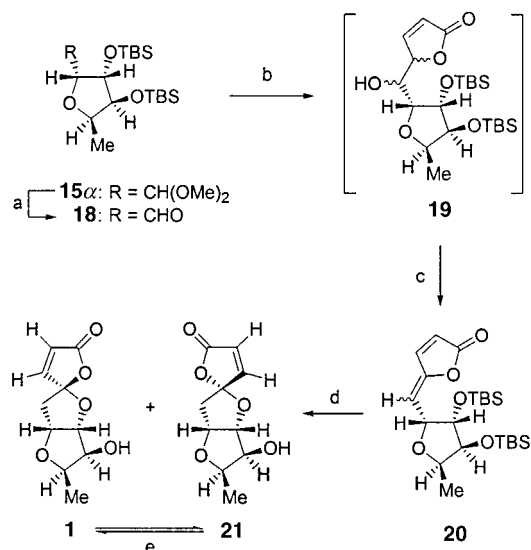
After screening a number of hypervalent iodine reagents, we converted the 6-deoxy-D-gulal derivative **12** into the corresponding C-furanoside **15** (Scheme 4) in high yield (88%) by using the reagent combination of iodosylbenzene and trifluoromethane sulfonic (triflic) anhydride (Tf₂O) in a solution of methanol and dichloromethane. In this reaction, dimethoxyiodosylbenzene^[11] and triflic acid are presumably generated as the active reagents *in situ* under anhydrous conditions. The presence of triflic acid is required for efficient ring contraction; the incorporation of an acid scavenger such as 2,4,6-tri-*tert*-butylpyridine rendered the reagent combination unreactive towards **12**.^[12] Moreover, the oxidative ring contraction proceeds with good stereoselectivity, yielding a 5:1 mixture of **15** in favor of the desired α -epimer (Scheme 4). Although ¹H NMR spectroscopic analysis of the 6-deoxygulal substrate **12** suggests that it approximates the ⁴H₅ conforma-



Scheme 4. Oxidative ring contraction.

tion,^[13] the half-chair conformational states are dynamic, and it is likely that the observed stereoselective formation of **15α** in the ring contraction arises from glycal activation via its ⁵H₄ conformation (i.e., Curtin–Hammett situation, Scheme 4). In this hypothesis, the favored approach of the I^{III} oxidant should occur on the α -face (**12** → **13**), an approach that would not only avoid steric interactions with the C6-methyl group, but would also lead to a chairlike transition state in the activation step to form **13**.^[14] Following a conformational chair flip (**13** → **14**) that orients the migrating C1–O bond antiperiplanar to the equatorial C2–I bond, ring contraction would ensue by means of the displacement of iodobenzene with inversion to provide **15α** as the major diastereomer. Conversely, β -approach of the oxidant onto **12** (⁴H₅) would also result in a chairlike transition structure; however, a higher energy transition structure might result as a consequence of a developing *syn*-pentane-like (i.e., 1,3-diaxial) interaction between the C4–O–TBS group and the C2–I^{III} substituent. Following a conformational chair flip (**16** → **17**), ring contraction would lead to the minor diastereomer **15β**.^[15, 16]

With an efficient synthetic route to the C-furanoside **15α**, introduction of the butenolide fragment and formation of the spiroketal functionality comprised the remaining steps in the synthesis of **1** (Scheme 5). The dimethyl acetal functionality in the α -epimer of **15** was hydrolyzed in the presence of TiCl₄ at 0 °C. This mild deprotection protocol afforded the tetrahydrofurfural intermediate **18** (88%) without epimerization of the C2 stereocenter and with the TBS protecting groups intact. Addition of commercially available 2-(trimethylsilyloxy)furan to the aldehyde **18** in the presence of BF₃·OEt₂ at -78 °C afforded a diastereomeric mixture of alcohols



Scheme 5. a) TiCl₄, Et₂O, 0 °C, 88%; b) 2-(trimethylsilyloxy)furan, BF₃·OEt₂, CH₂Cl₂, -78 °C; c) Burgess reagent, PhI, 55 °C, 80% (two steps); d) 1N LiOH_{aq}, 23 °C; 16% HF_{aq}, 23 °C, 93% (1:1.4, **1**/**21**); e) 8N HCl_{aq}, THF, 23 °C, quant.

19, which was directly treated with the Burgess dehydrating agent (MeO₂CNSO₂NEt₃) to afford the unsaturated γ -lactone **20** (80%, two steps) as a mixture of stereoisomers (2:1, *E/Z*). Formation of the spiroketal functionality and completion of the synthesis proceeded in a two-step, one-pot transformation from **20**, involving initial hydrolysis of the lactone (1N LiOH_{aq}), followed by acid-mediated (HF_{aq}) TBS-deprotection and spiroketalization to form a diastereomeric mixture of pyrenolide D (**1**) and its spiroketal epimer **21** in a 1:1.4 ratio (93% total). Although the thermodynamic distribution of **1** and **21** exhibits essentially no selectivity, separation of the epimers by chromatography is trivial, allowing the quantitative iterative re-equilibration of **21** (8N HCl_{aq}, THF) to enhance the production of the natural product **1**. The spectral data (¹H and ¹³C NMR, FTIR) of synthetic **1** derived from tri-*O*-acetyl-D-galactal coincide with those reported by Nukina and Hirota ([α]_D²³ = +64.3 (*c* = 0.4, CHCl₃), lit.: [α]_D²³ = +79.5 (*c* = 0.9, CHCl₃)).

In summary, the first synthesis of pyrenolide D (**1**) is described, involving a short sequence beginning with tri-*O*-acetyl-D-galactal. A key feature in the synthesis includes the efficient formation of highly functionalized tetrahydrofurfural intermediates directly from glycal substrates, by employing the reagent combination of iodosylbenzene and triflic anhydride in a mixture of methanol and dichloromethane. Not only did this process lead to the efficient synthesis and absolute stereochemical assignment of **1**, but it also highlights this oxidative ring contraction strategy as one that holds promise in both natural product and C-nucleoside synthesis.

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- [15] The employment of the *tert*-butyldimethylsilyl protecting groups was crucial in achieving the desired stereoselectivity. The use of dibenzyl-D-gual with the identical oxidative ring contraction procedure led to indiscriminate facial approach of the I^{III} reagent, affording a 1:1 (*α/β*) mixture of the corresponding tetrahydrofurfural acetals in 82% yield.
- [16] Formation of the minor diastereomer **15β** might also arise from the *β*-approach of the oxidant onto **12** (⁵H₄), leading to a higher energy twist-boatlike transition state. Following a conformational half-chair flip, ring contraction would lead to the minor diastereomer **15β**.

Crown-Ether-Directed Assembly of Discrete and One-Dimensional Silver Aggregates Containing Embedded Acetylenediide**

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In memory of Daniel Y. Chang

Recent studies have shown that the coordination modes of the acetylide dianion (C₂²⁻, IUPAC name acetylenediide) can be classified into three categories: 1) linear end-to-end

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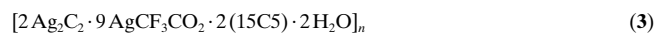
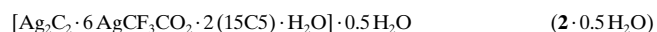
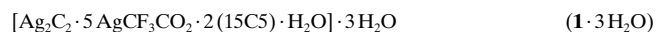
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bridging in the $[\text{AgC}_2]^-_\infty$ structure of ternary alkali metal silver acetylides MAgC_2 ($\text{M} = \text{Li, Na, K, Rb, Cs}$),^[1] 2) planar $\mu_4\text{-}\eta^1, \eta^2$ in the tetranuclear cation $[\text{Cu}_4(\mu\text{-dppm})_4(\text{C}_2)]^{2+}$ ($\text{dppm} = \text{bis}(\text{diphenylphosphanyl})\text{methane}$),^[2] 3) encapsulated inside a polyhedral Ag_n ($n = 6\text{--}9$) cage in a series of silver(I) double and triple salts.^[3]

Thus far all reported compounds in category 3) have either layer-type or three-dimensional network structures, in which the component $\text{C}_2@ \text{Ag}_n$ cages share common vertices or are linked by bridging anions. To obtain discrete molecules and infinite chains, our conceived strategy was to install protective cordons around the $\text{C}_2@ \text{Ag}_n$ moiety with neutral, multi-dentate ligands that can function as blocking groups or terminal stoppers.

Bearing in mind that ancillary ligation of solvent may lower the dimensionality of a coordination polymer, we introduced crown ether into silver acetylide containing systems in an attempt to prevent catenation and interlinkage of the silver polyhedra. Notably, in the context of host–guest complementarity,^[4,5] the interaction of Ag^{I} with crown ethers is rather weak: a) there is poor affinity between hard oxygen donor and soft cation, and consequently only a few silver(I)–crown ether complexes have been reported;^[6] b) the size of the Ag^{I} ion is too large to fit into the cavity of a crown ether, so that the host–guest system is necessarily forced to undergo distortion to accommodate the conflicting requirements of each partner.^[7] Accordingly, crown ethers are expected not to affect the formation of $\text{C}_2@ \text{Ag}_n$, but to act as weak capping ligands to provide ancillary ligation to the silver acetylide containing system. Herein we report the first isolation of discrete molecules and a zigzag coordination polymer containing embedded acetylide ions, for which [15]crown-5 (15C5) was employed as a structure-directing agent.

The crucial step in the synthesis of **1–3** took advantage of the fact that Ag_2C_2 readily dissolves in a concentrated aqueous solution of a silver(I) salt.^[8] Although the mechanism of the dissolution is not clear, it is presumable that the rigid lattice of Ag_2C_2 breaks down with compensation by multiple argentophilic interactions^[9] to form polyhedral species of the type $[\text{C}_2@ \text{Ag}_n]^{(n-2)+}$ ($n \geq 6$). The crown ether then influences the assembly process of these species during crystallization. Different preparative procedures have led to the isolation of discrete molecules **1** and **2** and a zigzag polymeric chain in **3**.



The sandwiched molecular structure of **1** is shown in Figure 1. The silver cage enclosing an acetylide dianion is in the shape of a pentagonal bipyramid, with its two apices (Ag6 and Ag7) slightly shifted to one side of the idealized molecular axis. The equatorial silver atoms lie within 0.205 Å of their least-squares plane. Four of the five edges of the equatorial pentagon are each bridged by one trifluoroacetate ligand (tfa), the $\text{Ag3} \cdots \text{Ag4}$ edge being the exception. Ag3 is coordinated by one aqua ligand, and the tfa

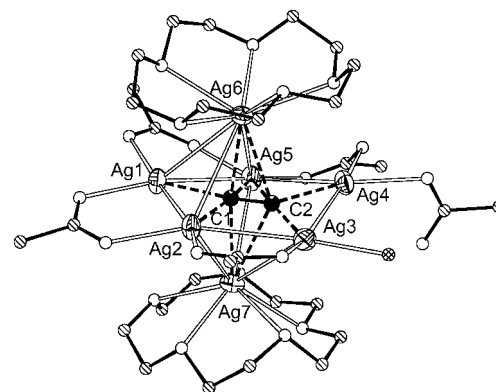


Figure 1. Crown-sandwiched molecular structure of compound **1** (the F and H atoms have been omitted for clarity). Range of metal–ligand distances [Å]: Ag–C 2.13–2.62; Ag–O 2.455–2.635 and 2.483–2.631 for the two crown ethers.

binding to Ag4 acts in a monodentate mode. Both Ag6 and Ag7 are each capped by one $\eta^5\text{-15C5}$ ligand, resulting in the first example of a discrete complex among silver acetylide containing systems.

Interestingly, the sandwich unit in **2** is very similar to that in **1**. As shown in Figure 2, it also takes the shape of a pentagonal

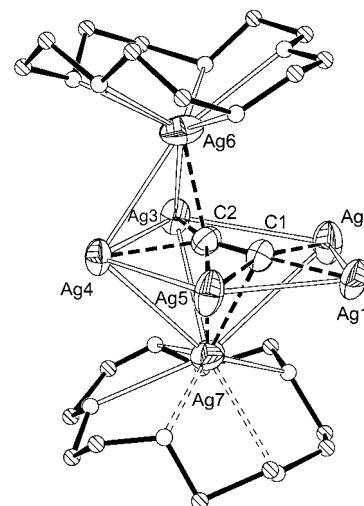


Figure 2. Sandwiched $\text{C}_2@ \text{Ag}_7$ unit in compound **2**. Metal–ligand distances [Å]: Ag–C 2.118–2.555; Ag–O (crown ether) 2.443–2.635 and 2.524–2.743 Å. Two longer Ag–O bonds that exceed 2.7 Å are represented by broken open lines.

bipyramid but the two apices (Ag6 and Ag7) undergo a much larger lateral shift. As a result of such a distortion, the C_2^{2-} ion exhibits only π interactions with Ag5 and Ag7 (C1 does not bind to Ag6). This is different from the case in **1**, where the C_2^{2-} ion has π interactions with Ag5 , Ag6 , and Ag7 . Another difference is that all edges of the equatorial pentagon in **2** are each bridged by one tfa ligand, and one corner atom is additionally coordinated by an aqua ligand. Two $[(\eta^5\text{-15C5})_2\text{-}(\text{C}_2@ \text{Ag}_7)(\mu\text{-CF}_3\text{CO}_2)_5(\text{H}_2\text{O})]$ moieties are connected through a central $[\text{Ag}_2(\text{tfa})_2]$ bridge to form a centrosymmetric hexadecanuclear supermolecule, as illustrated in Figure 3. Molecule **2** can be regarded as derived from **1** by linking two

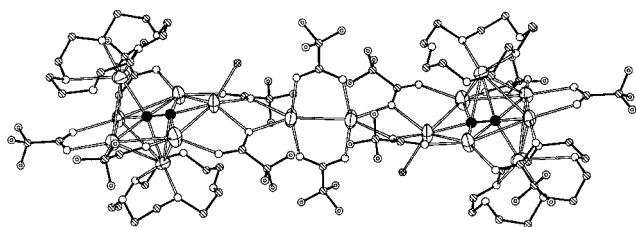


Figure 3. Centrosymmetric molecular structure of **2** (hydrogen atoms have been omitted for clarity): two sandwiched $C_2@Ag_7$ units and the central $[Ag_2(tfa)_2]$ bridge are linked by four μ_3 -tfa ligands.

$C_2@Ag_7$ units through $[Ag_2(tfa)_2]$ bridging, and steric crowding leads to serious distortion of the polyhedral cage in **2**.

In contrast to the single silver cage in **1** and **2**, compound **3** contains a novel tridecanuclear double cage composed of two distorted square antiprisms that share a common triangular face Ag1–Ag4–Ag5 (Figure 4). For the upper antiprism, atom

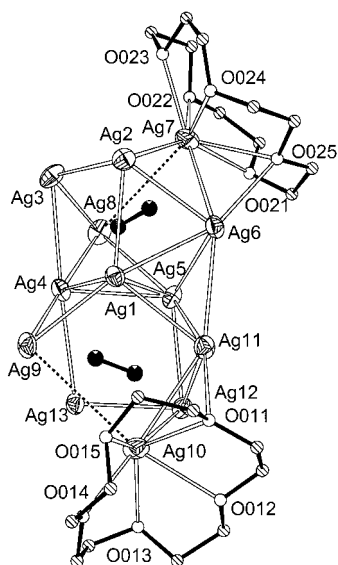


Figure 4. A sandwiched $(C_2)_2@Ag_{13}$ double-cage in **3**. Metal–ligand distances [Å]: Ag–C 2.12–2.70; Ag–O (crown ether) 2.416–2.694 and 2.437–2.696. The longer Ag...Ag distances that exceed 3.4 Å are represented by broken lines.

sets Ag1–Ag2–Ag3–Ag4 and Ag5–Ag6–Ag7–Ag8 constitute a pair of nearly parallel (dihedral angle 4.5°) tetragons, and for the lower one, the tetragons are made up of Ag4–Ag5–Ag12–Ag13 and Ag1–Ag9–Ag10–Ag11 (dihedral angle 3.5°). A unique feature is that both 15C5 ligands act in capping and bridging modes: for example, the upper 15C5 unit caps Ag7 and also bridges the Ag6...Ag7 edge through the binding of O025 to Ag6. Such a dual ligation mode is unprecedented in silver crown ether complexes. In the crystal structure of **3**, there are two nearly identical double cages in the asymmetric unit. As the molar ratio 15C5/ C_2^{2-} is 1:1 in **3**, in contrast to 2:1 in **1** and **2**, there is sufficient room around each $(C_2)_2@Ag_{13}$ double cage to allow the approach of bridging tfa groups in the assembly of an infinite zigzag chain.

The C_2^{2-} species in **1–3** all retain their triple-bond character with the C–C bond length ranging from 1.13(1) to 1.26(1) Å, which are close to those in acetylene (1.205 Å)^[10]

and CaC_2 (1.191 Å).^[11] The shortest Ag...Ag distances are 2.954(1) in **1**, 2.830(1) in **2**, and 2.847(1) Å in **3**, which are suggestive of significant argentophilic interactions.^[12]

In conclusion, the assembly process of an acetylide-encapsulating silver cluster in an aqueous system that contains Ag_2C_2 can be affected by the presence of a neutral, multidentate ligand like a crown ether, leading to the generation of unusual structures of low dimensionality. The present study has thus established a new direction in silver acetylide chemistry, showing that the $(\eta^5-15C5)Ag$ fragment is a potentially useful building block for the synthesis of silver clusters and supramolecular systems.

Experimental Section

Ag_2C_2 was prepared as described previously.^[3] **Caution:** Thoroughly dried Ag_2C_2 detonates easily upon mechanical shock and heating, and only a small quantity should be used in any chemical reaction.

1: Ag_2C_2 was added to a concentrated aqueous solution of $AgCF_3CO_2$ (1 mL) in a plastic beaker with stirring until saturation. The excess amount of Ag_2C_2 was filtered off, and a few drops of 15C5 were added to the filtrate. The resulting suspension was transferred to a thick-walled glass tube. The tube was subsequently flame-sealed and kept in a furnace at $115^\circ C$ for 6 h, and then cooled down to room temperature at $6 K h^{-1}$. Apart from a large quantity of black unidentified material, colorless platelike crystals of **1** were isolated in about 10% yield.

2: Ag_2C_2 was added to a concentrated aqueous solution of $AgCF_3CO_2$ and $AgBF_4$ (1 mL; molar ratio $\sim 1:1$) in a plastic beaker with stirring until saturation. The excess amount of Ag_2C_2 was filtered off, and a few drops of 15C5 ether were added to the filtrate. The resulting solution was allowed to stand without disturbance, and colorless blocklike crystals of **2** were obtained in over 50% yield after several hours.

3: Excess Ag_2C_2 and $AgCN$ were added to a concentrated aqueous solution of $AgCF_3CO_2$ and $AgBF_4$ (1 mL; molar ratio $\sim 1:1$) in a plastic beaker with stirring until saturation. After filtration, a few drops of 15C5 were added to the filtrate. The resulting solution was placed in a desiccator charged with P_2O_5 . The suspension that appeared overnight was transferred to a thick-walled glass tube. The tube was subsequently flame-sealed and kept in a furnace at $115^\circ C$ for 6 h, and then cooled down to room temperature at $6 K h^{-1}$. Colorless prismatic crystals of **3** were isolated in about 30% yield.

Crystal data for **1**: $C_{32}H_{33}Ag_7F_{15}O_{24}$, $M_r = 1841.67$, monoclinic, space group $P2_1/c$ (no. 14), $a = 20.772(1)$, $b = 12.0453(7)$, $c = 22.041(1)$ Å, $\beta = 94.612(1)^\circ$, $V = 5496.8(6)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 2.225 \text{ Mg m}^{-3}$, $F(000) = 3524$, $\mu(\text{Mo K}\alpha) = 2.566 \text{ mm}^{-1}$. 36540 reflections measured, 13197 unique ($R_{\text{int}} = 0.0774$), final $R1 = 0.0465$, $wR2 = 0.1011$ for 4820 observed reflections ($I > 2\sigma(I)$).

Crystal data for **2**: $C_{34}H_{43}Ag_8F_{18}O_{23.5}$, $M_r = 2032.64$, monoclinic, space group $P2_1/n$ (no. 14), $a = 10.7506(5)$, $b = 20.2915(9)$, $c = 26.468(1)$ Å, $\beta = 94.225(1)^\circ$, $V = 5758.2(5)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 2.345 \text{ Mg m}^{-3}$, $F(000) = 3892$, $\mu(\text{Mo K}\alpha) = 2.792 \text{ mm}^{-1}$. 38492 reflections measured, 13873 unique ($R_{\text{int}} = 0.0357$), final $R1 = 0.0561$, $wR2 = 0.1610$ for 7034 observed reflections ($I > 2\sigma(I)$).

Crystal data for **3**: $C_{42}H_{44}Ag_{13}F_{27}O_{30}$, $M_r = 2944.08$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 16.533(1)$, $b = 25.235(2)$, $c = 35.007(2)$ Å, $V = 14605(2)$ Å³, $Z = 8$, $\rho_{\text{calcd}} = 2.678 \text{ Mg m}^{-3}$, $F(000) = 11120$, $\mu(\text{Mo K}\alpha) = 3.547 \text{ mm}^{-1}$. 98895 reflections measured, 35210 unique ($R_{\text{int}} = 0.0481$), final $R1 = 0.0466$, $wR2 = 0.1051$ for 19902 observed reflections ($I > 2\sigma(I)$).

Data collection was performed at 293 K on a Bruker SMART 1000 CCD diffractometer using frames of oscillation range 0.3° , with $1.5^\circ < \theta < 28^\circ$. The structures were solved by direct methods, and all non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2 using the SHELXTL program.^[13]

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-152945 (**1**), CCDC-152946 (**2**), and CCDC-152947 (**3**). Copies of the data can be

obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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