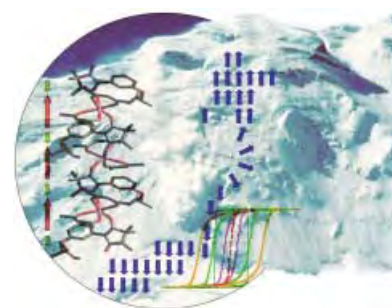


COVER PICTURE

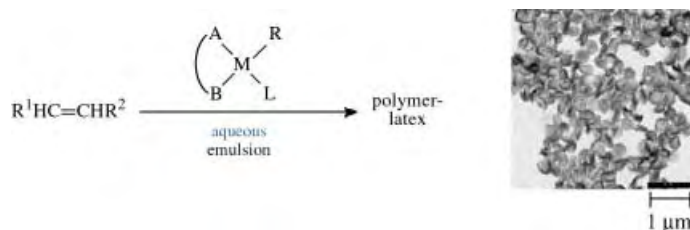
The cover picture shows a snow avalanche on the north face of Everest behind the structure of an enantiopure molecular ferromagnet which displays a rare phenomenon: a “magnetic avalanche”. The chiral complex $[\text{Mn}(\text{hfac})_2]$ ($S = \frac{1}{2}$, spins represented by the red arrows) with an enantiopure nitronyl nitroxide ligand ($S = \frac{1}{2}$, green arrows) exists as a coordination polymer (hfac = hexafluoroacetylacetonate). These chains are ferromagnetic (and are represented by the blue arrows), since the antiferromagnetically coupled organic- and metallic-centered spins do not compensate. At temperatures below 3 K these chains order magnetically and hysteresis loops open up. However, at 0.13 K (green curve) the width of the loop is smaller than at 0.3 K (orange curve). Thus, at a certain value of applied field there is an abrupt switching of some spins, which releases energy as a local heating. This heat initiates a switching of neighboring spins, which creates more heat and results in the magnetic equivalent of an avalanche. Further details about this optically active material are described by Veciana et al. on p. 586 ff. (Snow avalanche picture courtesy of Albert Castellet[®], and thanks to Pere Oller of the Institut Cartogràfic de Catalunya)



REVIEW

Contents

Water—a highly attractive, environmentally friendly reaction medium particularly for polymerization reactions. Whereas free-radical routes are well established, aqueous catalytic polymerization has seen major advances only recently. Numerous olefinic monomers can be transformed, for example, to aqueous polymer latices (see schematic reaction and picture).



Angew. Chem. **2002**, *114*, 564–582

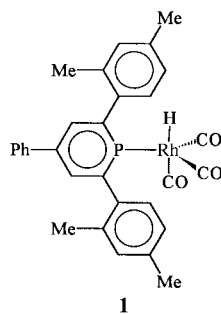
S. Mecking,* A. Held,
F. M. Bauers 544–561

Aqueous Catalytic Polymerization of
Olefins

Keywords: colloids • homogeneous
catalysis • polymerizations • polymer
latex • water chemistry

Molecules with low-coordinate phosphorus atoms were considered as a domain for basic researchers for three decades. They were studied as building blocks in element–organic synthesis or as ligands in coordination chemistry. In the last few years transition metal complexes with phosphabenzene and phospholyl ligands have attracted attention as components in efficient catalysts. Thus, **1** is an efficient hydroformylation catalyst. This account also covers the use of such complexes for C–C coupling reactions, polymerization, and asymmetric synthesis.

Angew. Chem. **2002**, *114*, 583–592



L. Weber* 563–572

Phosphorus Heterocycles: From Laboratory Curiosities to Ligands in Highly Efficient Catalysts

Keywords: asymmetric catalysis • homogeneous catalysis • hydroformylation • phosphaheterocycles • P ligands

HIGHLIGHT

More than 200 years after the discovery of the element oxygen, recent experimental studies at very large as well as extremely low pressures suggest the existence of molecular tetraoxygen O₄ as a possible new modification of oxygen.

Angew. Chem. **2002**, *114*, 593–594

O₂, O₃, O₄, ... O_n?

D. Schröder* 573–574

News about Oxygen

Keywords: allotropes • atmospheric chemistry • mass spectrometry • oxygen

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>

A Nanoporous Metal–Organic Framework Based on Bulky Phosphane Ligands

X. Xu, M. Nieuwenhuyzen, S. L. James* ◆

Surface Structure and Crystal Growth in Zeolite Beta C

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

Callipeltoside A: Assignment of Its Absolute and Relative Configuration by Total Synthesis

B. M. Trost,* O. Dirat, J. L. Gunzner ◆

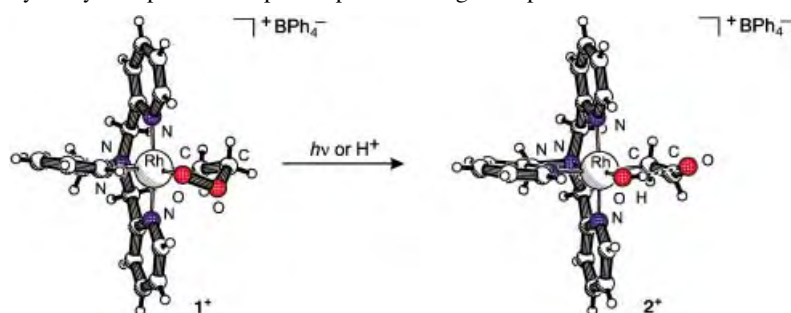
A New Catalyst for the Selective Oxidation of Butane and Propane

M. E. Davis,* C. J. Dillon, J. H. Holles, J. Labinger ◆

Surface Structure and Crystal Growth in Zeolite Beta C

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

Instead of direct conversion into a metal oxo complex and acetaldehyde or ethylene oxide, as was proposed earlier for 3-metalla-1,2-dioxolanes, 3-rhoda-1,2-dioxolanes **1**⁺ have now been found to rearrange to rhodium formylmethyl hydroxy complexes **2**⁺ upon exposure to light or protons.



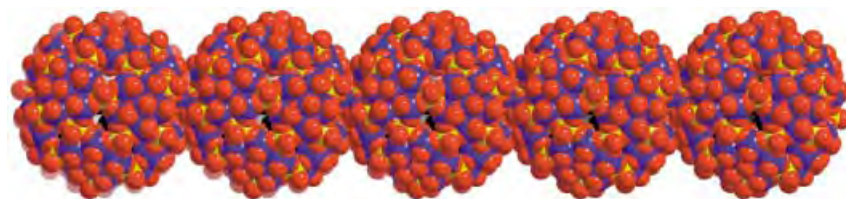
Angew. Chem. **2002**, *114*, 595–599

M. Krom, R. G. E. Coumans,
J. M. M. Smits, A. W. Gal* 575–579

Rearrangement of 3-Rhoda-1,2-dioxolanes to Rhodium Formylmethyl Hydroxy Complexes

Keywords: formylmethyl complexes • metallacycles • N ligands • photochemistry • rhodium

Crystal engineering with nanoobjects? Spherical structurally well-defined molybdenum-oxide-based giant clusters can be appropriately functionalized to a crystalline material with the remarkable property of having discrete cluster units which get covalently linked to form chains (see picture) through Fe–O–Mo bonds after having approached each other as a result of the release of crystal water upon drying.



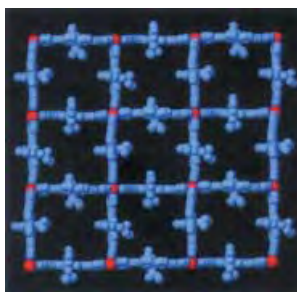
Angew. Chem. **2002**, *114*, 599–602

A. Müller,* S. K. Das,
M. O. Talismanova, H. Bögge,
P. Kögerler, M. Schmidtman,
S. S. Talismanov, M. Luban,
E. Krickemeyer 579–582

Paramagnetic Keplerate “Necklaces”
Synthesized by a Novel Room-Temperature Solid-State Reaction:
Controlled Linking of Metal-Oxide-Based Nanoparticles

Keywords: composites • magnetic properties • molybdenum • polyoxometalates • supramolecular chemistry

Use of a chiral, fluorene-based *N,N'*-bipyridine-type ligand (9,9-bis[(*S*)-2-methylbutyl]-2,7-bis-(4-pyridylethynyl)fluorene) with a Cu^{II} salt led to the formation of the first chiral non-interpenetrating square-grid coordination polymer (see picture). The free space in the polymer can be controlled by adjusting the size of the side chains attached to the ligand. The large channels and the incorporation of chirality into the polymer make such compounds strong candidates for chiral recognition applications.



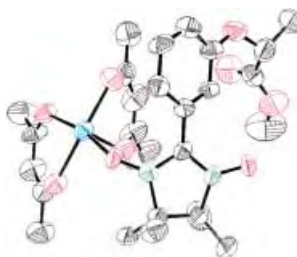
Angew. Chem. **2002**, *114*, 603–605

N. G. Pschirer, D. M. Ciurtin,
M. D. Smith, U. H. F. Bunz,*
H.-C. zur Loye* 583–585

Noninterpenetrating Square-Grid Coordination Polymers With Dimensions of 25 × 25 Å² Prepared by Using *N,N'*-Type Ligands: The First Chiral Square-Grid Coordination Polymer

Keywords: chirality • coordination polymers • copper • square grids

Magnetic avalanches: A chiral polymeric manganese(II) complex with an enantiopure nitronyl nitroxide ligand (see structure of repeating unit; red: oxygen, green: nitrogen, blue: manganese) shows unusual magnetic behavior. The polymer orders magnetically in the bulk at 3 K, and reveals unusual dynamic and hysteretic magnetic effects as well as a remarkable magnetic avalanche phenomenon below 0.3 K.



Angew. Chem. **2002**, *114*, 606–609

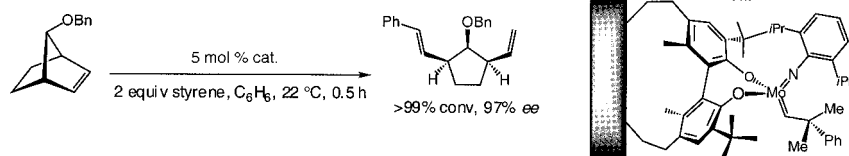
M. Minguet, D. Luneau,* E. Lhotel,
V. Villar, C. Paulsen, D. B. Amabilino,
J. Veciana* 586–589

An Enantiopure Molecular Ferromagnet

Keywords: chirality • ferromagnets • magnetic properties • manganese • O ligands • polymers



Substantially less toxic metal impurity than when unbound chiral complexes are used—this is achieved by the first polymer-supported chiral catalysts for olefin metathesis. These allow for efficient synthesis of various unsaturated carbo- and heterocycles in high optical purity through ring-opening (see scheme) and ring-closing reactions.



Angew. Chem. **2002**, *114*, 609–613

K. C. Hultsch, J. A. Jernelius,
A. H. Hoveyda,*
R. R. Schrock* 589–593

The First Polymer-Supported and
Recyclable Chiral Catalyst for
Enantioselective Olefin Metathesis

Keywords: asymmetric catalysis •
immobilization • metathesis •
molybdenum • solid-phase synthesis

A birefringent gel is formed when polycondensation of a strongly dipolar bis(trialkoxysilyl) compound is performed in an electric field. The birefringence is evidence for anisotropic ordering on the micrometer scale. The picture shows an image of the gel under a polarizing light microscope.



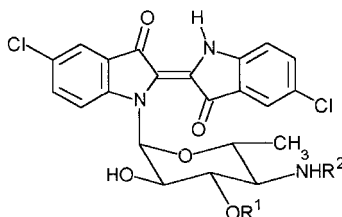
Angew. Chem. **2002**, *114*, 614–616

G. Cerveau, R. J. P. Corriu,* E. Framery,
S. Ghosh, M. Nobili 594–596

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

Keywords: birefringence • gels •
organic–inorganic hybrid composites •
self-assembly • sol–gel processes

Sky blue akashins (see picture) are the first indigoglycosides and the first natural derivatives of 5,5'-dichloroindigo to be isolated from terrestrial *Streptomyces*.



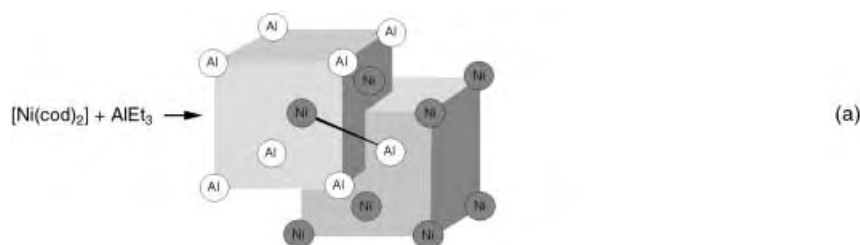
Angew. Chem. **2002**, *114*, 623–625

R. P. Maskey, I. Grün-Wollny,
H. H. Fiebig, H. Laatsch* 597–599

Akashins A, B, and C: Novel Chlorinated
Indigoglycosides from *Streptomyces* sp.
GW 48/1497

Keywords: antitumor agents •
glycosides • indigo • natural products

A fine powder of β -nickel aluminide NiAl is obtained by reaction of $[\text{Ni}(\text{cod})_2]$ (cod = cycloocta-1,5-diene) with AlEt_3 in toluene at room temperature and under a H_2 pressure of 5–10 MPa and subsequent distillation of the solvent, subsequent hydrogenation (0.1–5 MPa), and annealing (200°C) [Eq. (a)]. This novel wet chemistry synthesis of aluminides may be transferred to Ni_3Al (α -nickel aluminide) and ternary aluminide powders such as GaNiAl , FeNiAl , and CeNiAl .



Angew. Chem. **2002**, *114*, 628–632

H. Bönemann,* W. Brijoux,
H.-W. Hofstadt, T. Ould-Ely, W. Schmidt,
B. Waßmuth, C. Weidenthaler . 599–603

Wet Chemistry Synthesis of β -Nickel
Aluminide NiAl

Keywords: aluminum • intermetallic
phases • metal–metal interactions •
nickel • solid-state structures



Supramolecular tetrameric aggregates of four molecules of 7-deaza-2'-deoxyxanthosine are stabilized by unconventional C–H...O hydrogen bonds. In the solid state the tetramers stack to form a nanotube (see picture), in the center of which water molecules are found which are also stacked.



Angew. Chem. **2002**, *114*, 617–619

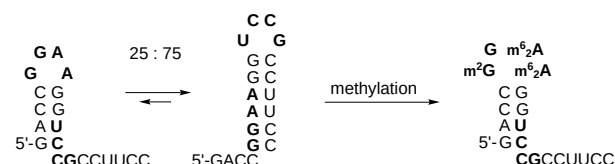
F. Seela,* T. Wiglenda, H. Rosemeyer,
H. Eickmeier, H. Reuter* 603–605

7-Deaza-2'-deoxyxanthosine Dihydrate
Forms Water-Filled Nanotubes with
C–H...O Hydrogen Bonds

Keywords: hydrogen bonds • nanotubes •
nitrogen heterocycles • nucleosides •
oligonucleotides



One sequence, but two conformations! The coexistence of conformers has been ascertained for a series of RNA oligonucleotides. The monomolecular conformation equilibria are shifted significantly by methylation of selected nucleobases; the methylation of the studied sequences corresponds to that of the naturally occurring helix 45 at the 3'-end in the small subunit of ribosomal RNA.



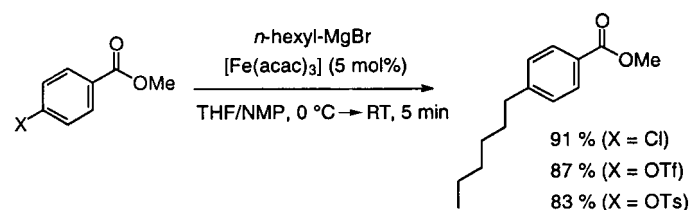
Angew. Chem. **2002**, *114*, 619–623

C. Höbartner, M.-O. Ebert, B. Jaun,
R. Micura* 605–609

RNA Two-State Conformation Equilibria
and the Effect of Nucleobase Methylation

Keywords: conformation analysis •
nucleosides • oligonucleotides •
RNA conformation equilibria •
RNA structures

Aryl chlorides are better substrates than the corresponding bromides or iodides in the presented cross-coupling with alkyl Grignard reagents that is catalyzed by iron salts (see scheme); even aryl tosylates are converted efficiently. This situation is attributed to a novel catalytic cycle, which probably involves iron complexes with formally negative oxidation states (probably Fe^{−II}).



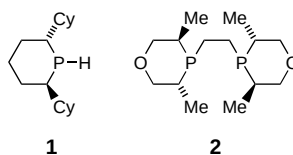
Angew. Chem. **2002**, *114*, 632–635

A. Fürstner,* A. Leitner 609–612

Iron-Catalyzed Cross-Coupling
Reactions of Alkyl-Grignard Reagents
with Aryl Chlorides, Tosylates, and
Triflates

Keywords: cross-coupling • Grignard
reagents • iron • magnesium •
organometallic compounds

Obvious but unknown in asymmetric catalysis were chiral six-membered-ring phosphanes and secondary phosphanes. As first examples of such ligands, oxaphosphinanes were now prepared and examined in asymmetric hydrogenation. With the monodentate oxaphosphinane **1**, for example, 96% *ee* was achieved with itaconic acid as the substrate and 97.5% *ee* was achieved with the chelate ligand **2** and 2-acetamidoacrylic acid as the substrate.



Angew. Chem. **2002**, *114*, 625–628

M. Ostermeier, J. Prieß,
G. Helmchen* 612–614

Mono- and Bidentate Phosphinanes—
New Chiral Ligands and Their
Application in Catalytic Asymmetric
Hydrogenations

Keywords: asymmetric catalysis • chelate
ligands • hydrogenation • phosphane
ligands • P ligands

Complementary strands and redox intercalators can be self-assembled into nanoscale structures capable of charge transfer at the electrode surface from DNA oligomers synthesized directly at covalently modified semiconductor silicon surfaces (see schematic representation).



A. R. Pike, L. H. Lie, R. A. Eagling, L. C. Ryder, S. N. Patole, B. A. Connolly, B. R. Horrocks, A. Houlton* .. 615–617

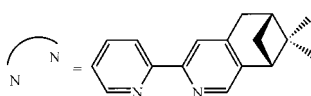
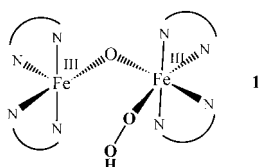
DNA On Silicon Devices: On-Chip Synthesis, Hybridization, and Charge Transfer

Keywords: charge transfer • DNA • molecular devices • semiconductors • silicon

Angew. Chem. **2002**, *114*, 637–639



In a spin: Transient peroxo iron complexes have been characterized by the means of Mössbauer and HF-EPR spectroscopies. Complex **1** has an unexpected $S=2$ ground state resulting from the coupling between the $S=5/2$ and $S=1/2$ iron(III) ions.



H. Hummel, Y. Mekmouche, C. Duboc-Toia, R. Y. N. Ho, L. Que, Jr., V. Schünemann, F. Thomas, A. X. Trautwein, C. Lebrun, M. Fontecave,* S. Ménage* ... 617–620

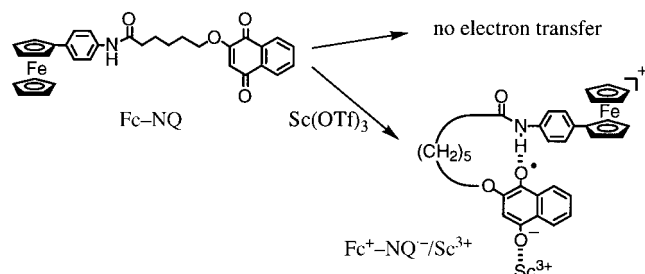
A Diferric Peroxo Complex with an Unprecedented Spin Configuration: An $S=2$ System Arising from an $S=5/2$, $1/2$ Pair

Keywords: EPR spectroscopy • iron • metalloenzymes • O–O activation • peroxo ligands

Angew. Chem. **2002**, *114*, 639–642



Initiated by metal ions: Intramolecular electron transfer in a donor–acceptor linked system (a ferrocene–naphthoquinone dyad Fc–NQ; see scheme) can be started thermally by adding an appropriate metal ion (Sc^{3+}) which can promote thermal electron transfer, which would otherwise be unlikely to occur, to give a radical ion complex ($\text{Fc}^+-\text{NQ}^-/\text{Sc}^{3+}$).



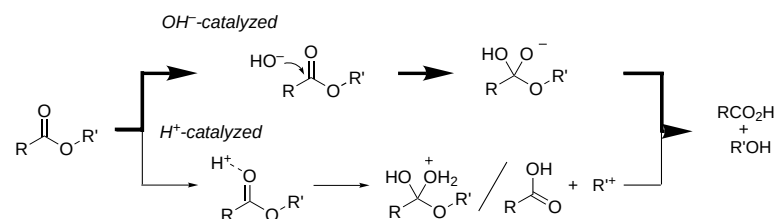
S. Fukuzumi,* K. Okamoto, H. Imahori* 620–622

Thermal Intramolecular Electron Transfer in a Ferrocene–Naphthoquinone Linked Dyad Promoted by Metal Ions

Keywords: electron transfer • ESR • ferrocene • kinetics • scandium

Angew. Chem. **2002**, *114*, 642–644

Not protons but hydroxide ions catalyze ester hydrolysis in supercritical water when the concentration of carboxylic acid generated by hydrolysis is low, as in the initial stage of the reaction. As the concentration of carboxylic acid increases with the progress of the reaction, the mechanism would become proton catalyzed (see scheme).



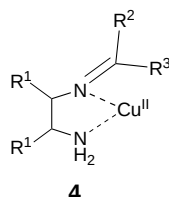
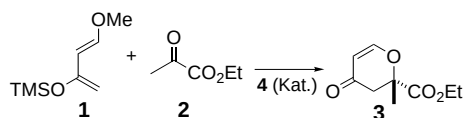
H. Oka, S. Yamago,* J. Yoshida,* O. Kajimoto* 623–625

Evidence for a Hydroxide Ion Catalyzed Pathway in Ester Hydrolysis in Supercritical Water

Keywords: esters • hydrolysis • kinetics • supercritical fluids

Angew. Chem. **2002**, *114*, 645–647

Only the correct order of addition of the components is required to prepare a variety of chiral Lewis acids. The complexes (for example, **4**) formed by the condensation of chiral, nonracemic 1,2-diamines with ketones and subsequent addition of $\text{Cu}(\text{OTf})_2$ (Tf = trifluoromethanesulfonyl) catalyze the cycloaddition reaction of Danishefsky's diene (**1**) and ethyl pyruvate (**2**) to form dihydropyrone (**3**).



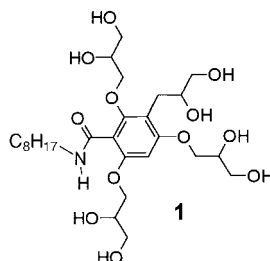
Angew. Chem. **2002**, *114*, 647–650

P. I. Dalko,* L. Moisan,
J. Cossy* 625–628

Modular Ligands for Asymmetric
Synthesis: Enantioselective Catalytic
 Cu^{II} -Mediated Condensation Reaction of
Ethyl Pyruvate with Danishefsky's Diene

Keywords: asymmetric catalysis • chiral
auxiliaries • cycloaddition • Lewis acids

A new mesophase, composed of closed spheroidal aggregates that contain lipophilic alkyl chains within a continuum of hydrogen-bonding networks, was realized with the low molecular weight amphiphile **1** in the absence of water or any other solvent.



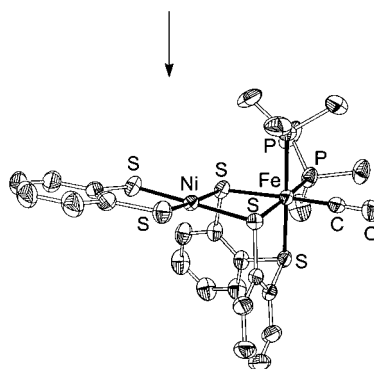
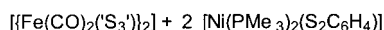
Angew. Chem. **2002**, *114*, 650–653

P. Fuchs, C. Tschierske,* K. Raith, K. Das,
S. Diele 628–631

A Thermotropic Mesophase Comprised of
Closed Micellar Aggregates of the
Normal Type

Keywords: amphiphiles • hydrogen
bonds • liquid crystals • mesophases •
micelles

Attempts to model the active sites of $[\text{NiFe}]$ hydrogenases have yielded numerous NiFe thiolate complexes but never a species with the characteristic $[(\text{RS})_2\text{Ni}(\mu\text{-SR})_2\text{Fe}(\text{CO})(\text{CN})_2]$ core. The $\text{Ni}^{\text{II}}/\text{Fe}^{\text{II}}$ title complex represents the PMe_3 derivative. Its $\nu(\text{CO})$ frequency of 1948 cm^{-1} corresponds to that of 1940 cm^{-1} for $[\text{NiFe}]$ hydrogenase in the Ni-R state.

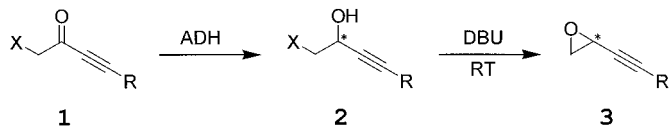


D. Sellmann,* F. Geipel, F. Lauderbach,
F. W. Heinemann 632–634

$[(\text{C}_6\text{H}_4\text{S}_2)\text{Ni}(\mu\text{-S}_3')\text{Fe}(\text{CO})(\text{PMe}_3)_2]$: A
Dinuclear $[\text{NiFe}]$ Complex Modeling the
 $[(\text{RS})_2\text{Ni}(\mu\text{-SR})_2\text{Fe}(\text{CO})(\text{L})_2]$ Core of
 $[\text{NiFe}]$ Hydrogenase Centers

Keywords: carbonyl ligands •
hydrogenases • iron • nickel • S ligands

Halogenated propargylic alcohol 2a ($\text{X} = \text{Cl}$, $\text{R} = \text{Ph}$) was prepared by the enzymatic reduction of the corresponding ketone **1a** with excellent enantioselectivity and chemical yield. Both enantiomers were synthesized with high total turnover numbers of the catalysts and cofactors. Other halogenated alkynones **1** were also suitable substrates for the enzymes. Alcohols **2** were converted into propargylic epoxides **3** under mild conditions to give multifunctionalized building blocks. $\text{X} = \text{Cl}$, Br ; $\text{R} = \text{H}$, Ph , trimethylsilyl, *tert*-butyldimethylsilyl; ADH = alcohol dehydrogenase; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



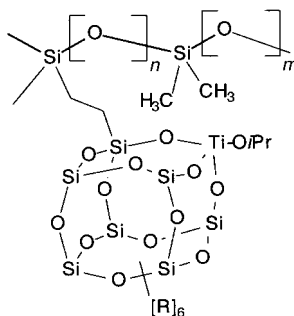
Angew. Chem. **2002**, *114*, 656–659

T. Schubert, W. Hummel,
M. Müller* 634–637

Highly Enantioselective Preparation of
Multifunctionalized Propargylic Building
Blocks

Keywords: asymmetric catalysis •
enzyme catalysis • epoxides • ketones •
oxidoreductases • reduction

Catalytic ensembles suitable for alkene epoxidation with aqueous hydrogen peroxide are now accessible. They are made by grafting robust titanium silsesquioxane sites onto dimethylsiloxane polymers (see picture) followed by cross-linking to three-dimensionally netted polymers.



M. D. Skowronska-Ptasinska,
M. L. W. Vorstenbosch, R. A. van Santen,
H. C. L. Abbenhuis* 637–639

Titanium Silsesquioxanes Grafted on Three-Dimensionally Netted Polysiloxanes: Catalytic Ensembles for Epoxidation of Alkenes with Aqueous Hydrogen Peroxide

Keywords: epoxidation • immobilization • silicon • silsesquioxanes • titanium

Angew. Chem. **2002**, *114*, 659–661



The structural diversity and marginal stability (5–15 kcal mol⁻¹) of proteins suggest the development of synthetic agents that selectively promote denaturation at low concentrations (see scheme). It is shown that an artificial receptor that binds tightly to the surface of native cytochrome *c* (cyt. *c*) lowers the melting temperature of the protein by 20°C at stoichiometric amounts; the receptor also selectively binds the native form rather than cyt. C551 and surface-modified cyt. *c*.



R. K. Jain, A. D. Hamilton* ... 641–643

Designing Protein Denaturants: Synthetic Agents Induce Cytochrome *c* Unfolding at Low Concentrations and Stoichiometries

Keywords: denaturation • molecular recognition • porphyrinoids • protein folding • protein surface

Angew. Chem. **2002**, *114*, 663–665



A short-circuited solid-state battery: A novel silveroxonickelate with the apparently innocent composition Ag_2NiO_2 (see structure: silver: white, nickel: dark gray, fluorine: black) shows a surprising charge distribution: subvalent silver atoms exist adjacent to rather highly oxidized nickel(III) centers. The compound is thus reminiscent of a short-circuited solid-state battery.



M. Schreyer, M. Jansen* 643–646

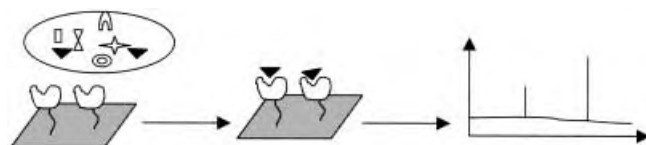
Synthesis and Characterization of Ag_2NiO_2 Showing an Uncommon Charge Distribution

Keywords: high-pressure chemistry • magnetic properties • nickel • silver • subvalent compounds • transition metal oxides

Angew. Chem. **2002**, *114*, 665–668



Simple and versatile: In a new assay for screening binding partners of proteins (see schematic representation), the target protein is first immobilized on a porous silicon probe, which is then incubated with a mixture of the possible binding partners. The captured binding partners are identified on-probe by means of laser desorption/ionization time-of-flight mass spectrometric analysis.



H. Zou,* Q. Zhang, Z. Guo, B. Guo,
Q. Zhang, X. Chen 646–648

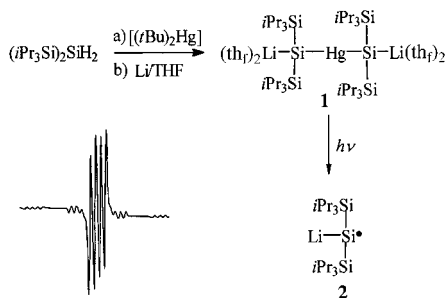
A Mass Spectrometry Based Direct-Binding Assay for Screening Binding Partners of Proteins

Keywords: analytical methods • biosensors • drug research • immobilization • mass spectrometry • silicon

Angew. Chem. **2002**, *114*, 668–670



Radical developments in silyllithium chemistry: The preparation and X-ray structure of **1**, the first compound with geminal Hg-Si-Li bonding, is reported. Compound **1** is obtained by the reaction of $(i\text{Pr}_3\text{Si})_2\text{SiH}_2$ with $[(t\text{Bu})_2\text{Hg}]$ followed by lithiation in THF. Irradiation of **1** produces $[\text{Li}(i\text{Pr}_3\text{Si})_2\text{Si}]^\bullet$ (**2**), the first silyl radical with an α -Si-Li bond detected by EPR spectroscopy (see spectrum).



D. Bravo-Zhivotovskii,* M. Yuzevovich, N. Sigal, G. Korogodsky, K. Klinkhamer, B. Tumanskii, A. Shames, Y. Apeloig* 649–651

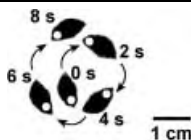
The Synthesis of the First Compound with Li-Si-Hg Bonding: $[\text{Li}(i\text{Pr}_3\text{Si})_2\text{Si}]^\bullet$ —a Source for the $[\text{Li}(i\text{Pr}_3\text{Si})_2\text{Si}]^\bullet$ Radical

Keywords: EPR spectroscopy • lithium • mercury • radicals • silicon

Angew. Chem. 2002, 114, 671–673



The artificial millimeter-scale “autonomous movers” glide across the surface of a liquid without an external power source. This system is based on a combination of two processes: Motion of individual objects powered by the catalytic decomposition of hydrogen peroxide, and relative motion (self-assembly) caused by capillary interactions at the fluid/air interface. The picture shows the rotational/translational motion of a single object; the motion of a pair of these object depends on their chirality.



R. F. Ismagilov, A. Schwartz, N. Bowden, G. M. Whitesides* 652–654

Autonomous Movement and Self-Assembly

Keywords: autonomous movement • complexity • energy-dissipating systems • self-assembly

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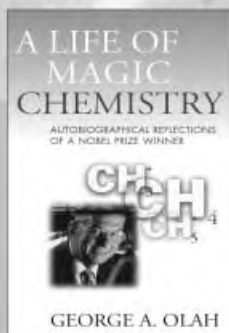
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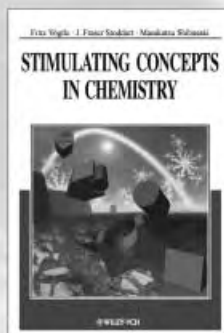
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Aqueous Catalytic Polymerization of Olefins

Stefan Mecking,* Anke Held, and Florian M. Bauers

Catalytic conversions in aqueous environments by transition metal complexes have become a well-established field over the past two decades. However, the vast majority of investigations have focussed on small-molecule synthesis. This may appear somewhat surprising as water is a particularly attractive reaction medium, especially for polymerization reactions. For example, aqueous emulsion and suspension polymerization is carried out today on a large scale by noncatalytic free-radical routes. Polymer latices can be obtained as a product, that is, stable aqueous dispersions of polymer particles in the size range of 50 to 1000 nm.

Such latices possess a unique property profile. Amongst other advantages, the use of water as a dispersing medium is particularly environmentally friendly. In comparison to these free-radical reactions, aqueous catalytic polymerizations of olefinic monomers have received less attention. However, considerable advances and an increased awareness of this field have emerged during the past few years. A variety of high molecular weight polymers ranging from amorphous or semicrystalline polyolefins to polar-substituted hydrophilic materials have now been prepared by catalytic polymerization of olefinic monomers in water. Polymer

latices based on a number of readily available monomers are accessible and catalytic activities as high as 10^5 turnovers per hour have already been reported. As another example, materials prepared by aqueous catalytic polymerization have been investigated as protein inhibitors. A versatile field spanning colloids, polymer, and coordination chemistry has emerged.

Keywords: colloids • homogeneous catalysis • polymerizations • polymer latex • water chemistry

1. Introduction

Aqueous catalytic polymerization may seem like a contradiction at first sight. The high water sensitivity of Ziegler or Phillips catalysts applied commercially for the production of polyolefins is well known. However, water offers a unique combination of properties as a medium for polymerization reactions:

- A high heat capacity, which enables an effective transfer of the heat of polymerization.
- A high polarity that results in a markedly different miscibility with many monomers and polymers compared to organic solvents.
- Surfactants can effectively stabilize dispersions of hydrophobic polymer particles in water towards aggregation.
- Water is nonflammable and nontoxic.

The versatile opportunities resulting can be illustrated by the following noncatalytic free-radical polymerization procedures.

1.1. Aqueous Free-Radical Polymerization

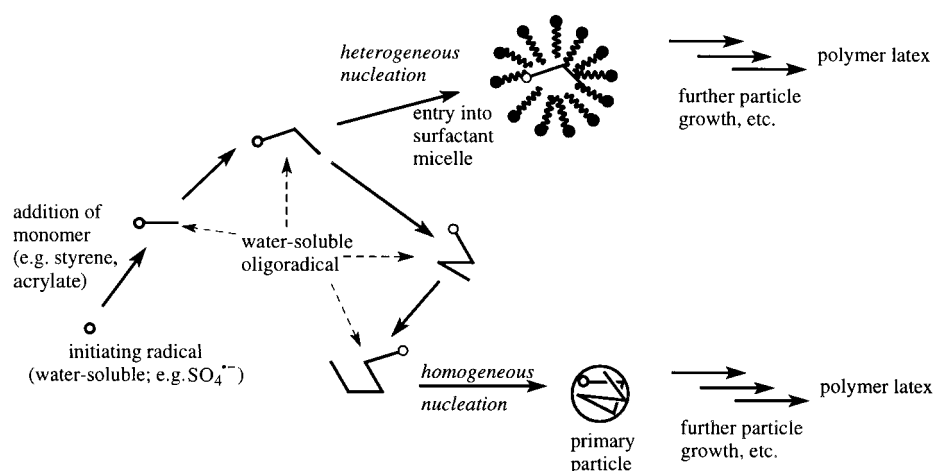
Free radical initiated emulsion polymerization is applied today on a multimillion ton scale.^[1–4] Originally, emulsion polymerization of styrene and butadiene was developed independently in the United States and in Germany in the 1940s to obtain a substitute for natural rubber during wartime. Today, vinyl acetate, acrylic acid and its esters, butadiene, and styrene comprise the most important monomers for emulsion polymerization.

Polymer latices are obtained as products of emulsion polymerization. A polymer latex is a stable dispersion of polymer particles in the size range of 50 to 1000 nm in a liquid medium, usually water. Latices are also called polymer dispersions. In such latices, coagulation and precipitation of the polymer particles must be prevented. Stabilization can occur by different mechanisms: by electrostatic stabilization (most often involving ionic surfactants adsorbed to the particle surface), or by steric stabilization (for example, by

[*] Dr. S. Mecking, Dr. A. Held, Dipl.-Chem. F. M. Bauers
Institut für Makromolekulare Chemie und
Freiburger Materialforschungszentrum der
Albert-Ludwigs-Universität Freiburg
Stefan-Meier-Strasse 31, 79104 Freiburg (Germany)
Fax: (+49) 761-203-6319
E-mail: stefan.mecking@makro.uni-freiburg.de

means of water-soluble polymers adsorbed or covalently bound to the particle surface). The mechanism of emulsion polymerization is complex and, despite intense research, many details are still subject to debate. In addition, as a consequence of the different mechanisms of chain growth, chain initiation, and chain transfer in free-radical versus catalytic polymerization, insights gained from the former can not be transferred directly to catalytic polymerizations. Nonetheless, a strongly simplified representation can be useful to illustrate underlying principals.

A typical polymerization mixture initially consists of water, emulsified water-immiscible monomer, surfactant, and a water-soluble initiator. A water-soluble radical, for example, $\text{SO}_4^{\cdot-}$ generated from $\text{K}_2\text{S}_2\text{O}_8$, grows by addition of monomer dissolved in small amounts in the aqueous phase (Scheme 1). The resulting water-soluble oligomeric radical can grow until it reaches a critical chain length at which it becomes insoluble and collapses upon itself ("homogeneous nucleation"). The resulting primary particle is stabilized by adsorption of surfactant, and further polymerization within the particle results in particle growth. Alter-



Scheme 1. Simplified schematic representation of possible mechanisms for particle formation in free-radical emulsion polymerization.

nately, the water-soluble oligomer can enter a surfactant micelle prior to reaching its critical chain length, thus generating a particle ("heterogeneous micellar nucleation"). The emulsified monomer droplets serve as a reservoir for monomer during emulsion polymerization, but as alluded to previously polymerization usually does not occur in these droplets but in the polymer particles to which the monomers diffuse (Scheme 2). (A different situation is encoun-

Stefan Mecking, born October 1966, studied chemistry at RWTH Aachen. In 1994 he received his Ph.D. degree there in the group of W. Keim with a thesis on small-molecule catalysis by palladium complexes with hemilabile ligands. After an 18-month postdoctoral stay in the group of M. Brookhart (University of North Carolina at Chapel Hill) as a Feodor-Lynen Fellow, he joined the corporate research of Hoechst AG in Frankfurt in 1996 as a research chemist heading a laboratory in the polymers group. In 1998 he moved to Freiburg University, where he is currently working on his habilitation.

In addition to aqueous catalytic polymerizations, his research interests include catalytically active colloidal polymer/metal hybrids. Recently, he received the Eugen-Graetz Award of Freiburg University in recognition of the latter work.

Anke Held, born in Berlin in 1974, studied chemistry in Marburg. After her diploma thesis with W. Heitz in 1998 she moved to Freiburg to join the group of S. Mecking for her dissertation on catalytic aqueous polymerizations by cationic palladium(II) complexes. She recently obtained her Ph.D. degree under the guidance of R. Mülhaupt, and now works for Basell in Ludwigshafen (Germany).

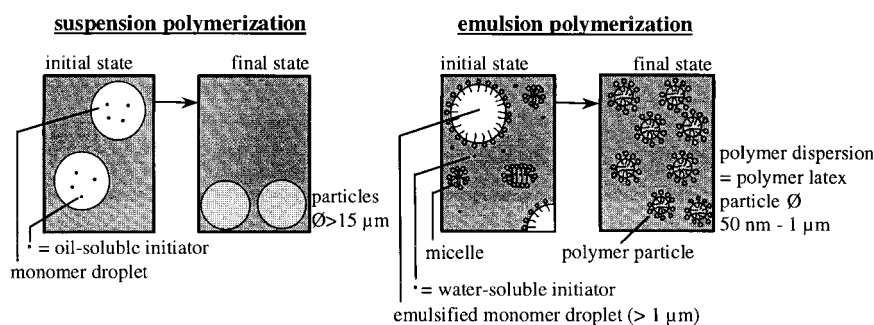
Florian M. Bauers, born in Berlin in 1974, studied chemistry in Freiburg. In 2000, he concluded these studies with a diploma thesis on nickel(II)-catalyzed aqueous ethylene polymerization. Since then he has continued this work in his dissertation. In recognition of his outstanding diploma, he was recently awarded the Steinhöfer Prize.



F. M. Bauers

A. Held

S. Mecking



Scheme 2. Schematic representation of free-radical emulsion and suspension polymerization.

tered in the special case of miniemulsion polymerization, see Section 3.) In this respect, the term “emulsion polymerization” can be misleading. In regard to nomenclature, the term “polymerization in emulsion” is frequently used in this review to describe a (catalytic) polymerization carried out under emulsion conditions. This is intended to make no implications about the mechanism of particle formation, which has often not been investigated; also it is not implied whether stable polymer latices were formed or not.

The viscosity of the reaction mixture increases only to a relatively small extent during emulsion polymerization. The viscosity of an aqueous latex is much lower than of a solution of the polymer in an organic solvent. Thus, high polymer yields can be achieved during emulsion polymerization in a given amount of reaction volume. The polymer latices obtained can be precipitated to isolate the polymer, but for many applications they are used as such, for example, in paints and coatings. In such applications film formation is a key step. Evaporation of the dispersing medium results in formation of a continuous polymer film on the substrate. Several million tons of water are evaporated annually by this, and the nonflammability and environmental friendliness of water are particularly advantageous. In addition to existing large-scale applications in paints, coatings, adhesives, paper manufacturing, and other industries, polymer dispersions also possess an interesting potential as submicron-size carrier materials, for example, for biomedical applications^[5] or as catalyst supports.^[6–9] Polymer latices can also represent the substrates for polymer-analogous modification (namely, synthetic transformations employing a polymer as a substrate).^[10, 11] The previous considerations show that polymer latices not only represent a convenient opportunity for a polymer supplier to “sell large amounts of water to the customer”^[12] along with the polymer, but offer unique advantages regarding applications and the polymerization process.

In suspension polymerization a water-insoluble olefinic monomer is also polymerized. Typically, a mixture of water, water-immiscible monomer, monomer-soluble initiator, and optionally a stabilizer is stirred vigorously. Polymerization occurs in the monomer droplets (Scheme 2). The particles obtained are much larger ($>15\ \mu\text{m}$) than in emulsion polymerization, and they do not form stable latices, but instead precipitate during polymerization. For example, the polystyrene beads used for the well-known ion-exchange resins can be prepared by suspension polymerization.^[13] In

this review, the designation of a catalytic polymerization as “suspension-type” should merely indicate a polymerization of a water-insoluble monomer to a polymer which separates during the polymerization, usually in the absence of any stabilizer.

In dispersion polymerization a soluble monomer is polymerized to an insoluble polymer, which forms a stable latex. With particle sizes of about 1 to $15\ \mu\text{m}$, dispersion polymerization can cover the particle size range between emulsion and suspension polymerization.

Aqueous solution polymerization is also well-known, in which a water-soluble monomer is polymerized to a water-soluble polymer.^[14] For example, acrylic acid is produced on a large scale by free-radical techniques in this manner.^[15] Again, the nonflammability and nontoxicity of water as well as its high heat capacity are advantageous. In some cases performing polymerizations in homogeneous solution can also allow for an increased control of the molecular weight compared to multiphase polymerizations (see Section 6).

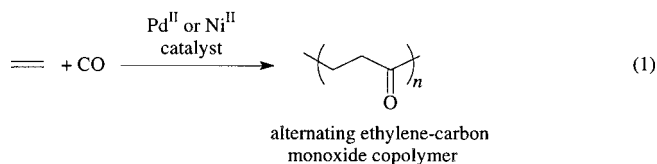
1.2. Transition Metal Catalysis in Aqueous Media

In contrast to the aforementioned large-scale free-radical polymerizations, transition metal catalyzed coordination polymerization reactions in water have been little investigated. The early transition metal catalysts^[16–19] used almost exclusively in commercial catalytic polymerization of olefins are extremely sensitive to moisture. What factors govern the reactivity and stability of a given catalyst towards water? Metal complex catalyzed conversions of olefinic substrates to low molecular weight products or to polymers generally involve organometallics, most often with metal–alkyl bonds, as the active species. Availability of coordination sites for substrate binding is a general prerequisite for catalytic transformations. In regard to catalysis in aqueous media, water can hydrolyze metal–alkyl bonds, block coordination sites by binding as a ligand, and attack coordinated olefin monomers or other ligands.^[20] Regarding the former two—perhaps most crucial—aspects, complexes of late transition metals are much less sensitive than early transition metal compounds because of their lower oxophilicity. This stability towards water is illustrated impressively by the large-scale commercial application of the Ruhrchemie–Rhone Poulenc process^[21] in which propylene is hydroformylated using a rhodium catalyst in a biphasic aqueous system. In this process a simple separation of the water-soluble catalyst from the apolar products is enabled. A variety of low molecular weight compounds has been prepared by aqueous-phase organometallic catalysis, and such reactions can by no means be regarded as exotic today. By comparison, catalytic polymerizations in water have received little attention. In Cornils and Herrmann’s comprehensive book^[21] on aqueous-phase organometallic chemistry, the preparation of polymers covers only a minor portion.^[22]

However, carrying out catalytic polymerizations in water is an attractive goal. The previous considerations on free-radical aqueous polymerizations illustrate the unique advantages of water as a reaction medium, and catalytic polymerization offers access to many polymer microstructures which can not be prepared by free-radical techniques. Considerable advances have been achieved over the last few years in the area of aqueous catalytic polymerization. This trend can be related to general advances in late transition metal catalyzed olefin polymerization, an increasing need for environmentally friendly products and processes—and perhaps also simply to a fascination with this topic and the opportunities resulting from the combination of polymer, organometallic, and colloid chemistry. It can be noted that other non-free-radical routes, namely polycondensation^[23] and ionic polymerization^[24–27] in aqueous emulsion have also received increasing interest recently. Also, metal-mediated reactions such as polymerization by Suzuki coupling in aqueous solution,^[28, 29] aqueous atom-transfer radical polymerization (ATRP),^[30–32] and polymerization of acetylenes^[33, 34] have recently been studied. This paper reviews aqueous catalytic polymerization of olefinic monomers. To exploit its aforementioned unique properties, the presence of water as a major constituent of the reaction medium is usually required, consequently catalytic polymerizations in organic solvents in the presence of only minor amounts of water are excluded. In comparing catalyst activities throughout this review, it should be noted that these data were determined under strongly varying conditions by different authors. Therefore, they should be taken only as an indication of the order of magnitude. The same holds true for polymer molecular weights. Activities are given as turnover per hour (TOh^{-1} ; $\text{TO} = \text{mol substrate converted per mol of metal}$) so as to enable a comparison of polymerization of different monomers (with different molecular weights) and of catalysts based on different metals.

2. Copolymerization of Carbon Monoxide with Olefins

Catalytic olefin–CO copolymerization has found widespread interest as a consequence of the use of cheap starting materials and the materials properties of the copolymers.^[35–37] As a result of the mechanism of the reaction, polyketones with a strictly alternating sequence of units derived from olefin and CO are obtained [Eq. (1)]. An alternating ethylene–CO copolymer melts at 257 °C. Incorporation of propylene

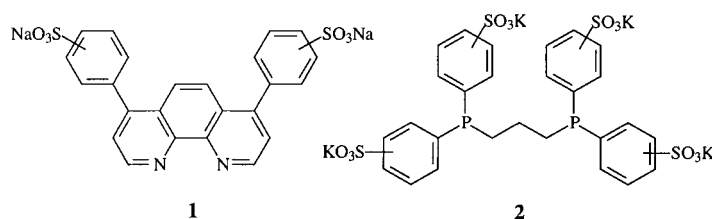


decreases the melting point, thus enabling the processing of the materials (for example, 6 mol % propylene: T_m 220 °C).^[43] Such semicrystalline ethylene-propylene-carbon monoxide

terpolymers have been commercialized by Shell since 1995 as a new engineering thermoplastic under the tradename Carilon, and BP has developed similar materials termed Ketonex.^[38, 39] However, Shell has recently announced it will abandon this business for undisclosed reasons.^[40] The polyketones have a good resistance to hydrocarbon solvents and good abrasion properties.^[41] As a drawback, the presence of a large number of carbonyl groups renders the polymers sensitive to UV light; furthermore undesired crosslinking through condensation reactions can occur at high temperatures during processing. These materials are unique in the sense of representing a commercially available olefin polymer with a large number of oxygen-containing polar moieties, prepared by coordination polymerization.

In regard to the catalyst systems used, a major breakthrough has been the finding that catalysts based on cationic palladium(II) complexes with bidentate ligands exhibit substantially increased activities in ethylene–carbon monoxide copolymerization compared to previously known systems.^[42, 43] In addition to diphosphanes, a variety of bidentate ligands based on nitrogen^[44, 45] and other donor atoms^[46] has been found to be suitable for olefin–CO copolymerizations. Methanol is typically used as the reaction medium, which demonstrates the stability of these catalysts towards protic media.^[47]

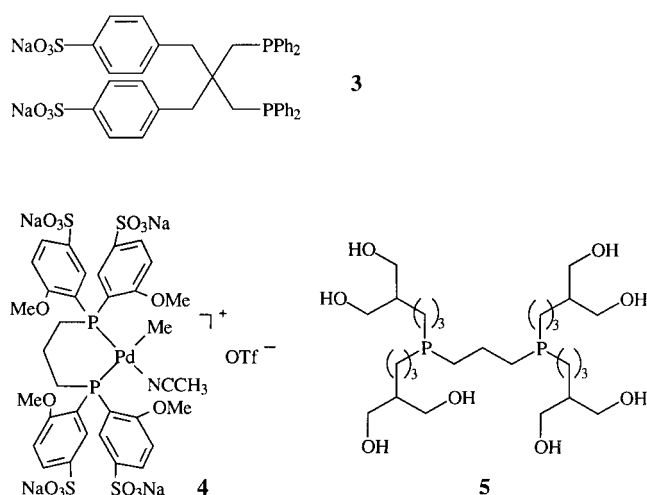
The first investigation of a catalytic olefin–CO copolymerization employed water as a reaction medium! In a patent filed in 1948, Reppe and Magin described the reaction of ethylene with carbon monoxide in the presence of an aqueous solution of potassium tetracyanonickel(II)ate at 150 °C and 150 bar.^[48] Along with oligomers of the general structures $\text{H}[\text{CH}_2\text{CH}_2\text{C}(=\text{O})]_n\text{C}_2\text{H}_5$ and $\text{H}[\text{CH}_2\text{CH}_2\text{C}(=\text{O})]_n\text{OH}$ ($n = 1, 2$), higher molecular weight solid “polyketones” were obtained. This reaction is a very early example, in a general sense, of an aqueous catalytic olefin “polymerization”.^[49] More recently several reports on ethylene–CO copolymerization in water as a reaction medium have appeared that have been catalyzed by cationic palladium complexes with water-soluble bidentate ligands (for the solubility of the monomers in water see ref. [50]). Sen et al. observed moderate activities of up to about 10^2 TOh^{-1} in ethylene–CO copolymerization with the sulfonated phosphane- or nitrogen-based ligands **1** and **2**. The reaction conditions are rather mild



compared to those used in the work of Reppe and Magin, the reaction being carried out at 50 °C and 35 bar each of ethylene and CO (reaction time of 22 h with the in situ catalyst $[\text{Pd}^{\text{II}}(\text{NCCH}_3)_4](\text{BF}_4)_2$ bidentate ligand). An alternating propylene–CO copolymer with a molecular weight of $1.4 \times$

10^4 g mol^{-1} (versus polystyrene standards) was also prepared, albeit at lower rates.^[51]

Sheldon et al. reported significantly higher activities of up to $1.5 \times 10^4 \text{ TO h}^{-1}$ for aqueous ethylene–CO copolymerization with a very similar catalyst system comprising the same ligand **2**.^[52] These higher activities, comparable to those observed with 1,3-bis(diphenylphosphanyl)propane (dppp) as the non-sulfonated model for **2** in non-aqueous polymerization in methanol, were ascribed to a higher purity of the sulfonated phosphane ligand and the addition of a Brønsted acid which increased catalyst stability. The molecular weights of the copolymer at $M_w \leq 5 \times 10^4 \text{ g mol}^{-1}$ and $M_w/M_n \approx 2$ were found to be similar to materials obtained in methanol as a non-aqueous reaction medium under otherwise comparable conditions. A high catalyst stability in the aqueous reaction is evidenced by a constant productivity over several hours.^[52, 53] A variation of the ligand “backbone” utilizing different chain length ($\text{ArP}_2(\text{CH}_2)_n\text{PAr}_2$ with $n = 2$ to 5) showed the best results in terms of activity and polymer molecular weight were obtained with $n = 3$ (**2**).^[53] This trend is similar to non-aqueous polymerizations in methanol, that is, apart from solubility issues, no requirements specific to the ligand structure are evident for this particular catalyst system for aqueous polymerizations. Specially designed water-soluble ligands with two sulfonated moieties attached to the C_3 ligand backbone (**3**),^[54] or hydroxylated neutral ligands such as **5**^[55] were found to afford higher activities than **2**.



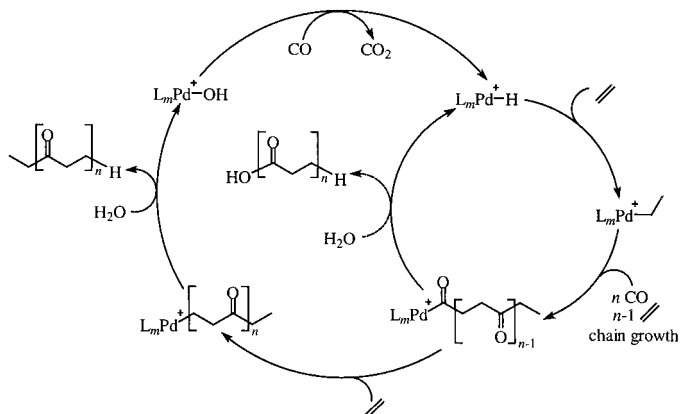
The introduction of methoxy substituents at the *ortho* position of the aryl rings of a diphosphane-modified cationic palladium catalyst results in markedly increased catalyst performance.^[47] Ethylene–CO copolymers with molecular weights of up to $M_w \leq 1.2 \times 10^5 \text{ g mol}^{-1}$ at narrow polydispersities ($M_w/M_n \approx 2$) were obtained in the aqueous polymerization with the fully *o*-OMe-substituted analogue of ligand **2**. High activities of $6.1 \times 10^4 \text{ TO h}^{-1}$ have been reported when a well-defined complex **4** of this ligand was used (90°C , 60 bar ethylene/CO 1/1, 1 h reaction time).^[56]

As alluded to earlier, the properties of ethylene–CO copolymers can be varied by introduction of another olefin as a termonomer, and 1-olefin–CO copolymers are also well-known. The properties of these copolymers depend strongly on their composition. Thus, the glass transition temperature of

1-olefin–CO copolymers decreases from room temperature to nearly -60°C upon increasing the chain length of the 1-olefin from propylene to 1-dodecene.^[37] By contrast to polar ethylene–CO copolymers, copolymers with higher 1-olefins display a hydrophobic character. Ethylene-1-olefin-CO terpolymers and 1-olefin-CO copolymers can be prepared in aqueous polymerizations.^[51, 54, 55] Catalysts with entirely alkyl-substituted diphosphane ligands such as **5** (by comparison to the phenyl substituents in dppp) are particularly well-suited for 1-olefin copolymerization.^[55]

In the aforementioned copolymerization reactions, the polyketone was reported to precipitate during the reaction.^[53–55] However, in the presence of an emulsifier such as sodium dodecyl sulfate (SDS) and under otherwise suitable conditions, stable polymer latices can be obtained. Such polymerizations can be carried out with water-soluble catalysts based on, for example, ligands of type **5**.^[57] By using a miniemulsion technique (see Section 3) non-water-soluble catalysts can also be employed.^[58] Stable latices of ethylene–undec-10-enoic–carbon monoxide terpolymers ($M_w = 7 \times 10^4 \text{ g mol}^{-1}$ versus PMMA standards) and of 1-olefin–CO copolymers ($M_w = 2 \times 10^4 \text{ g mol}^{-1}$) have been prepared. The carboxylic acid functions as a polymerizable stabilizer. Hereby, modification of the diphosphane ligands to attain water solubility is not necessary, and thus can reduce synthetic effort. With their glass transition occurring below room temperature, 1-olefin-CO copolymers are well suited for film formation. Latices with high solids contents can be prepared.

The mechanism of chain growth by alternating insertion of ethylene and CO into Pd-acyl and Pd-alkyl species during aqueous polymerization is identical to the well-investigated copolymerization in methanol. A significant difference is represented by hydrolysis as an important chain-transfer step: methanolysis of a Pd-alkyl species affords a Pd–OMe species which initiates chain growth during non-aqueous polymerization and results in the formation of a new $\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{OMe}$ end group in the polymer. By contrast, hydrolysis affords a Pd–OH species, which reacts with CO to form a palladium hydride prior to initiation of the next chain (Scheme 3). Therefore, polyketones with two keto end groups are obtained preferentially or exclusively in the aqueous reaction.^[52, 54, 59] The aforementioned reaction can be regarded as a “reactivation” pathway after hydrolysis of a metal–alkyl bond which is specific to aqueous reactions involving CO.



Scheme 3. Mechanism of aqueous ethylene–CO copolymerization.

From the data available it can be concluded that aqueous ethylene–CO copolymerization can occur at rates similar to the commercially viable process performed in methanol. High molecular weight polyketones can be obtained. Apparent advantages of water as a reaction medium for such polymerizations are its nonflammability and environmental friendliness. The recently demonstrated accessibility of stable latices may enable new applications, which also do not require processing at disadvantageously high temperatures.

3. Polymerization of Ethylene and 1-Olefins

Ziegler or Phillips catalysts based on early transition metals (Ti, Zr, Cr, V) are employed in the commercial production of polyolefins.^[16–19] However, as a result of their high oxophilicity, such catalysts require strictly anhydrous conditions. In recent years, the discovery of several new types of catalysts for ethylene and 1-olefin polymerization based on late transition metals have spurred a strong interest in this area.^[18,60–62] As a consequence of their lower oxophilicity, such catalysts can be much more stable towards polar media.

It can be noted, that latices of low-density polyethylene (LDPE) are prepared as a specialty product by free-radical emulsion polymerization.^[63] However, one of the disadvantages this process suffers from is the necessity of working at very high pressures (2000 bar) and a low variability regarding the tailoring of the polymer microstructure.

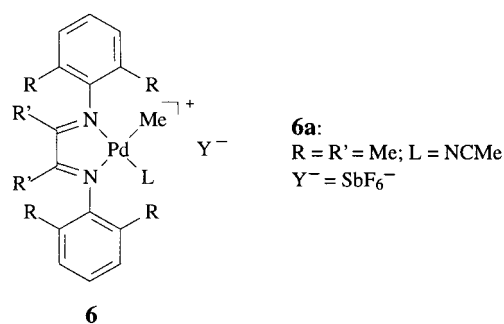
An ethylene polymerization in water by a well-defined rhodium complex, $[(N\text{---}N\text{---}N)RhMe(OH_2)(OH)]^+$, was reported by Flood and co-workers in 1993 ($N\text{---}N\text{---}N=1,4,7$ -trimethyl-1,4,7-triazacyclononane). Throughout this review, $X\text{---}Y$ or $X\text{---}Y\text{---}Z$ denotes a bidentate and a tridentate ligand, respectively, which coordinates through the X, Y, and Z atoms).^[50,64] A low molecular weight polyethylene was obtained ($M_w=5 \times 10^3 \text{ g mol}^{-1}$) at room temperature and 60 bar ethylene after 90 days of reaction. Although the reaction rates of 1 TO per day were extremely low, this finding was an important precedence for aqueous catalytic ethylene polymerization. Interestingly, undesired hydrolysis of the Rh–alkyl bond could be observed at higher temperatures as a reaction competing with chain growth.

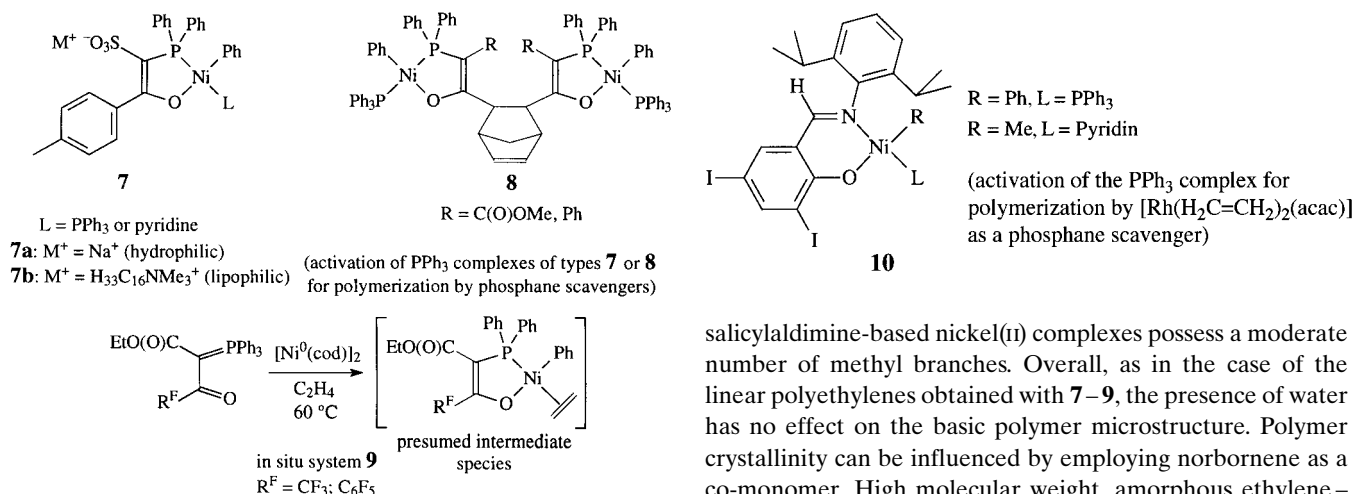
In 1995 Brookhart and co-workers reported that cationic diimine-substituted palladium complexes of type **6** can polymerize ethylene to high molecular weight, highly branched material in organic solvents such as dichloromethane. The unique structure of the ethylene homopolymers obtained

results from a propensity of the metal centers to “run” along the growing polymer chain between insertions.^[65, 66] In an extensive patent on these polymerization reactions McLain and co-workers demonstrated with several examples that these can also be carried out in water.^[67] Detailed investigations by Mecking and co-workers revealed that the catalyst is remarkably stable in this suspension-type aqueous polymerization.^[68, 73] Ethylene is polymerized at a steady rate over a time period of 16 h or longer. Activities of 900 TO h^{-1} , similar to non-aqueous polymerization in dichloromethane, are observed at slightly elevated ethylene pressures of 20 bar with **6a**. However, this high stability is attributed to an “encapsulation” of the water-insoluble catalyst in the growing hydrophobic polymer, which protects the catalyst from access of water. Accordingly, aqueous solutions of water-soluble catalysts with sulfonate-substituted diimine ligands are inactive for ethylene polymerization.^[69] Mechanistic studies revealed that a complex of type **6** is stable in a water-containing solution, that is, neither the Pd–Me moiety nor the diimine ligand are hydrolyzed. However, decomposition occurred instantaneously upon addition of ethylene.^[68] It is also of interest in the context of aqueous polymerization whether water can compete with the monomer for binding to the metal center and thus block coordination sites necessary for polymerization. Addition of ethylene to the water complex $[(N\text{---}N)PdMe(OH_2)]^+$ at -40°C resulted in clean conversion to the known^[65] ethylene complex $[(N\text{---}N)PdMe(H_2C=CH_2)]^+$.^[70, 73] This result indicates that water does not have a significant propensity for blocking the coordination sites in this cationic palladium system.

Polymerization by **6a** in aqueous suspension yields a rubbery amorphous solid ($M_w=2 \times 10^5 \text{ g mol}^{-1}$, $M_w/M_n=2$ to 3, ca. 70 branches per 1000 carbon atoms, $T_g=45^\circ\text{C}$) while a traditional polymerization in dichloromethane under similar reaction conditions (temperature, ethylene pressure) leads to a highly viscous liquid polyethylene ($M_w=3 \times 10^4 \text{ g mol}^{-1}$, ca. 100 branches per 1000 carbon atoms, $T_g=70^\circ\text{C}$). However, rather than a conceivable direct interaction of water with the catalyst, this effect appears to be related to the different phases encountered by the catalyst during polymerization (heterogeneous aqueous suspension of polymer encapsulating the catalyst instead of a homogeneous solution).^[68] It can be noted that ethylene polymerization by **6** represents a catalytic aqueous synthesis of a hyperbranched polyolefin.^[70, 71] Polymerization of 1-olefins by catalysts of type **6** in aqueous emulsion has been claimed to afford stable latices.^[72]

In view of many potential applications, synthesis of a largely linear polyethylene with some degree of crystallinity in aqueous emulsion would be of interest. Very recently, Mecking and co-workers and Spitz and co-workers independently reported the nickel(II)-catalyzed polymerization of ethylene to linear material in aqueous emulsion.^[73, 74] Neutral nickel(II) complexes **7** and **8** (Scheme 4) based on known bidentate P --- O ligands^[75–78] were found to be suited as catalyst precursors. Stable latices of low molecular weight polyethylene could be obtained with water-soluble catalyst precursors **7a**:^[73, 79, 80] for example, a dispersion of polyethylene with $M_w=3 \times 10^3 \text{ g mol}^{-1}$ and $M_w/M_n=2–3$ was ob-





Scheme 4. Neutral nickel(II) complexes utilized for the polymerization of ethylene in aqueous emulsion.

tained with 10^3 TO h^{-1} under moderate reaction conditions (70°C , 50 bar ethylene pressure). The catalysts are stable in the aqueous polymerization for several hours. Significantly higher activities of up to about $3 \times 10^4 \text{ TO h}^{-1}$ were observed with **8** in aqueous emulsion, however, the latices prepared with these lipophilic catalyst precursors were reported not to be stable.^[74, 81] Catalyst activities and polymer molecular weights are reduced in the aqueous polymerizations relative to those observed in traditional polymerization in non-aqueous organic media such as toluene. The lower activities and molecular weights can be related, to a large extent, to a lower rate of chain growth in the aqueous polymerization caused by an insufficient local concentration of ethylene at the catalytically active centers.^[79] Good catalyst activities at limited ethylene concentrations can be expected to be advantageous on catalyst performance.^[82]

Claverie and co-workers have obtained highly active catalysts by introducing electron-withdrawing perfluorinated substituents to the bidentate P⁺O ligand (**9**; Scheme 4).^[83, 84] Low molecular weight linear material ($M_w = 3 \times 10^3 \text{ g mol}^{-1}$) can be obtained at impressive rates of up to $1.7 \times 10^5 \text{ TO h}^{-1}$ in aqueous emulsion at ethylene pressures of 25 bar.

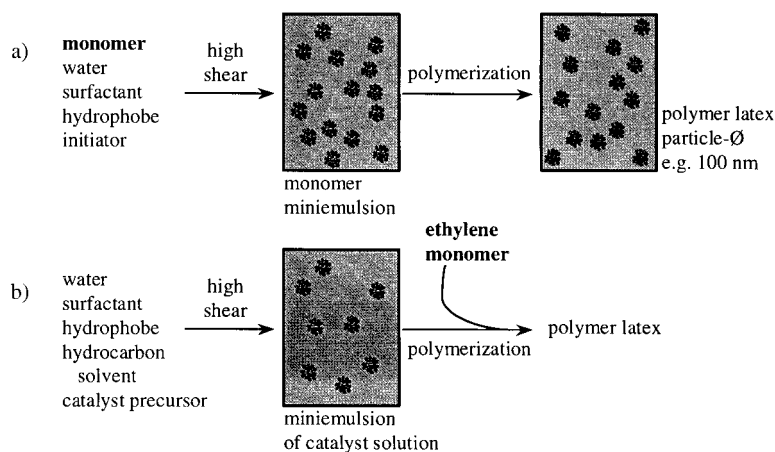
High molecular weight polyethylene has been prepared in aqueous polymerizations with a different class of catalysts.^[79, 88] In traditional polymerization in toluene, suitable representatives of the aforementioned P⁺O-substituted catalysts and recently reported N⁺O-substituted salicylaldimine-based catalysts are known to afford polymers of similar maximum M_w values.^[62, 76, 77, 85–87] However, by contrast to the previously discussed aqueous polymerizations with P⁺O-substituted catalysts, the latter type of complexes was found to yield high molecular weight material also in aqueous polymerization. Semicrystalline polyethylenes of $M_n \leq 10^5 \text{ g mol}^{-1}$ with narrow polydispersities ($M_w/M_n = 2–4$) are accessible in a suspension-type polymerization with precursors **10**. Although these catalysts display a limited stability to water, activities of $3 \times 10^3 \text{ TO h}^{-1}$ at room temperature are observed. Like the polymers obtained in traditional polymerization in organic solvents, the materials obtained in water with

salicylaldimine-based nickel(II) complexes possess a moderate number of methyl branches. Overall, as in the case of the linear polyethylenes obtained with **7–9**, the presence of water has no effect on the basic polymer microstructure. Polymer crystallinity can be influenced by employing norbornene as a co-monomer. High molecular weight, amorphous ethylene–norbornene copolymers which form films at room temperature can be obtained in aqueous polymerizations.^[79]

The synthesis of stable latices requires suitable nucleation of primary particles and subsequent stabilization. Water-soluble initiators are used in classical free-radical emulsion polymerization. Chain growth initially affords water-soluble oligomeric radicals, which can nucleate particles by collapsing upon themselves or by entering a surfactant micelle (see Section 1). Similar considerations appear reasonable for the aforementioned catalytic polymerization to form stable latices with the water-soluble complex **7a**.^[73, 79] As a different strategy, a very fine initial dispersion of a hydrophobic catalyst precursor can be achieved as a solution in a large number of toluene/hexadecane miniemulsion droplets (diameter ca. 100 nm), dispersed in the continuous aqueous phase.^[83, 88]

Miniemulsions^[89–91] can be prepared by subjecting a mixture of water, a surfactant, an organic phase, and a so-called hydrophobe to high shear. High shear results in the formation of very small droplets. These are stabilized against Ostwald-ripening^[92] to larger droplets by the hydrophobe. Miniemulsions can be stable over prolonged periods of time. Free-radical miniemulsion polymerization has been investigated extensively. It should be noted, that the catalytic polymerization reactions of ethylene discussed in the following section differ from typical free-radical polymerization of a preformed miniemulsion of a liquid monomer (Scheme 5). Gaseous ethylene monomer is fed continuously to the reaction mixture after miniemulsification of the catalyst solution. Thus, polymerization of preformed miniemulsion droplets of monomer to particles of the same size, a typical feature of “mini-emulsion polymerization”, does not apply.

The strategy of using a catalyst miniemulsion for latex synthesis offers two advantages: catalyst precursors do not have to be modified hydrophilically, which often reduces synthetic effort,^[83] and somewhat water-sensitive precursors can be applied.^[88] Claverie et al. have prepared stable latices of low molecular weight linear polyethylene at high polymerization rates by using miniemulsions of the aforementioned catalysts of type **9**.^[83] Latices of ethylene copolymers with 1-olefins have also been prepared.^[93] In addition to the various attractive aspects of polymerization in emulsion, another significant advantage is relevant in such copolymerizations: in conventional ethylene copolymerizations using



Scheme 5. Comparison of typical free-radical miniemulsion polymerization of a liquid monomer (a) with the particular case of catalytic polymerization of ethylene using a miniemulsion of a catalyst solution (b).

late transition metal catalysts in organic media, the incorporation of 1-olefins is usually low and requires the addition of large amounts of the co-monomer. In emulsions, the high local concentration of the liquid co-monomer in droplets can enable high levels of co-monomer incorporation. Copolymerization of ethylene with comonomers bearing polar, hydrophobic moieties is of strong interest in the context of polymer latices. To date, ethylene copolymerization with undec-10-en-1-ol has been reported briefly.^[93]

In the aforementioned ethylene polymerizations yielding stable latices low molecular weight polymer was obtained. The synthesis of dispersions of polyolefins with higher molecular weights is necessary to exploit the property profile of polymer latices. Bauers and Mecking have employed miniemulsions of the somewhat water-sensitive catalyst precursor **10** ($R = \text{Me}$, $L = \text{pyridine}$) for ethylene polymerization. Hereby, stable latices of high molecular weight semicrystalline polyethylene ($M_n = 10^5 \text{ g mol}^{-1}$, $M_w/M_n = 2-4$) could be obtained.^[88]

The polyethylene latices obtained in the different emulsion polymerization procedures using the various aforementioned nickel(II) complexes display particles with average diameters of 100 to 600 nm. A number of anionic surfactants or neutral stabilizers are suitable, that is, compatible with the catalysts and capable of stabilizing the latex. Solids contents of up to 10% have been reported to date. A typical transmission electron microscopy (TEM) image is shown in Figure 1. By comparison to the smooth, spherical latex particles of amorphous polystyrene, as an example of a well-studied hydrocarbon polymer prepared by free-radical emulsion polymerization, the ruggedness of the particles shown can be rationalized by their high degree of crystallinity.

Very recently, an aqueous olefin polymerization using an early transition metal catalyst has also been reported.^[94] A solution of styrene in toluene is prepolymerized briefly by a catalyst prepared by the combination of $[(C_5Me_5)Ti(OMe)_3]$ with a borate and an alkylaluminum compound as activators. The reaction mixture is then emulsified in water, where further polymerization occurs to form syndiotactic polystyrene stereoselectively. It is assumed that the catalyst is

contained in emulsified droplets and is thereby protected from the access of water, with the formation of a crystalline polymer enhancing this effect. Cationic or neutral surfactants were found to be suited, whereas anionic surfactants deactivated the catalyst. The crystalline polystyrene formed was reported to precipitate from the reaction mixture as relatively large particles of 500 μm .

A number of catalytic aqueous ethylene polymerizations have been reported very recently. A particularly interesting aspect is the successful synthesis of latices of largely linear polyethylenes. Copolymerization with various olefinic monomers enables a control of the polymer crystallinity. High catalyst activities have already been achieved in the synthesis of latices of low molecular weight material. Such polymerizations can be of interest as a

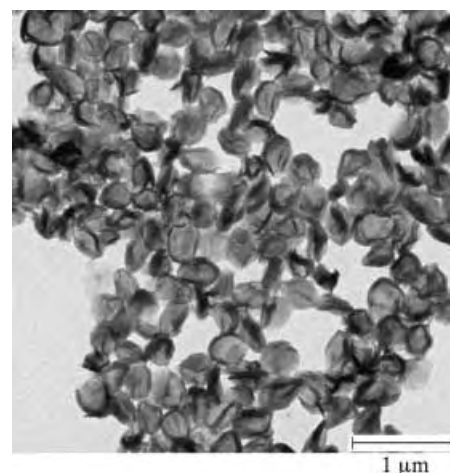


Figure 1. TEM micrograph of polyethylene latex particles prepared by catalytic polymerization ($M_w = 2.1 \times 10^5 \text{ g mol}^{-1}$, $M_w/M_n = 2.2$; crystallinity 54%; catalyst precursor **10** ($R = \text{Me}$, $L = \text{pyridine}$)).^[88]

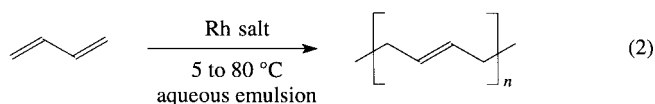
convenient direct route to wax dispersions. The accessibility of latices of high molecular weight polyethylene has also been demonstrated. Further improvements of catalyst activities are clearly an important aim in this field. The role of small amounts of added organic solvents, for example, in the miniemulsion technique, on catalyst performance remains to be clarified. The aforementioned activities reported to date for aqueous ethylene polymerization (10^5 TO h^{-1}) are lower than those of metallocenes as single-site catalysts used for the commercial production of polyolefins ($> 10^7 \text{ TO h}^{-1}$).^[95] Ziegler catalysts, including metallocenes, have been improved continuously with enormous efforts over the past 50 years. In view of potential applications, it is debatable whether catalyst activities in aqueous polymerizations must rival those of today's polyolefin production, or whether restrictions are not quite as stringent as in today's polyolefin industry. As an example of properties interesting for potential applications, polyolefins contain a negligible portion of double bonds compared to styrene-butadiene copolymers, a hydrocarbon-polymer currently prepared by free-radical emulsion poly-

merization on a large scale. This lower level of double bonds can result in a considerably higher stability of polymer films formed from polyolefin latices towards UV light and air.

4. Polymerization of Conjugated Dienes

Free-radical polymerization of butadiene in aqueous emulsion is performed on a large scale. Butadiene–styrene copolymer latices are employed, for example, in paper treatment.^[2] Transition metal catalyzed polymerization of dienes in non-aqueous media is equally important. *cis*-1,4-Polybutadiene rubbers are produced with Ziegler-type catalysts based on titanium, cobalt, nickel, or neodymium in solution processes with aromatic hydrocarbon solvents.^[106]

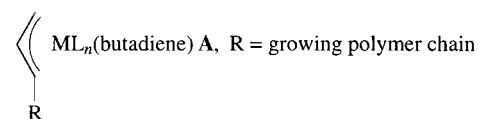
Polymerization of butadiene catalyzed by rhodium salts in water as a reaction medium was already reported in the 1960s by Rinehart et al. and Canale and co-workers. By utilizing $\text{Rh}^{\text{III}}\text{Cl}_3 \cdot 3\text{H}_2\text{O}$ as a catalyst precursor butadiene is polymerized stereoselectively in aqueous emulsion to semicrystalline *trans*-1,4-polybutadiene exclusively [Eq. (2); >99% *trans*].^[50, 96, 97] By comparison, free-radical polymeriza-



tion of butadiene in aqueous emulsion typically yields polymers with 60% *trans*-incorporated units under similar conditions.^[98] Polymerization of butadiene in water as a reaction medium by salts of late transition metals other than rhodium was reported to yield polybutadienes of other microstructures, however, the data provided is very limited.^[97]

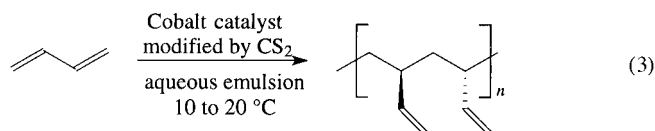
Polymer molecular weights of $2.6 \times 10^4 \text{ g mol}^{-1}$ were determined by light scattering measurements.^[97] The catalyst activity was virtually constant over 30 h at 50 °C, which demonstrates there is a remarkably high stability of the catalyst in the aqueous polymerization.^[99] Anionic emulsifiers, namely SDS or alkylbenzene sulfonates, were found to be suitable.^[96, 100] On the basis of polymer microstructure and comparative experiments with radical inhibitors, a coordination polymerization mechanism was suggested. A free-radical polymerization mechanism can be excluded. Rhodium(I) species, formed by the reduction of the Rh^{III} salts used as the catalyst precursors by the butadiene monomer, have been suggested as the active species. In agreement with this, Rh^{I} complexes such as $[\text{Rh}_2\text{Cl}_2(\text{C}_4\text{H}_6)_3]$ are also active catalysts with moderate activities of up to about $2 \times 10^3 \text{ TO h}^{-1}$ (with formic acid as a co-catalyst).^[101, 102] In contrast to industrially important free-radical copolymerization, styrene is not incorporated in the rhodium-catalyzed butadiene polymerization.^[103] The rhodium catalyst is also inactive towards isoprene,^[101, 103] whereas other authors have reported polymerization of *cis*- or *trans*-1,3-pentadiene in aqueous emulsion.^[104] Only limited data is available regarding the stability and other properties of the polymer dispersions obtained. Precipitation of considerable portions of the polymer has been mentioned at high conversions in the polymerization of butadiene.^[99, 105]

The growing polymer chain in the polymerization of dienes by late transition metal complexes is generally assumed to coordinate to the metal center in a η^3 -allyl fashion (**A**).^[106] Allyl complexes are generally considered to be quite stable



compared to other organometallic compounds, particularly to alkyl compounds.^[107] Thus, it is perhaps not surprising that the coordination polymerizations of dienes in water were discovered relatively early on.

Polymerization of butadiene by modified cobalt catalysts, such as the *in situ* system $[\text{Co}^{\text{III}}(\text{acac})_3]/\text{AlEt}_3/\text{H}_2\text{O}/\text{CS}_2$ (acac = acetylacetonate), can yield highly crystalline syndiotactic 1,2-polybutadiene ($T_m = 205^\circ\text{C}$).^[108] The high stereoselectivity of these catalysts has been ascribed to coordination of carbon disulfide as a ligand to the metal center.^[109] Such stereospecific polymerizations can be carried out in aqueous emulsion,^[110–112] and polymer latices can be obtained [Eq. (3)].^[111] A “prepolymerization” with a small portion of

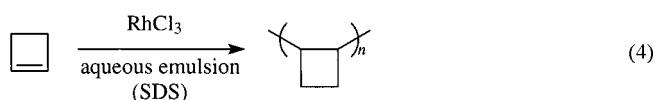


butadiene monomer in the presence of only trace amounts of water is required. A solution of this “prepolymerized” catalyst mixture in a hydrocarbon is subsequently dispersed in water together with further butadiene, and the polymerization then proceeds. It has been speculated that the catalytically active species is shielded from the access of water by the polymer formed during the prepolymerization.^[110]

The aforementioned catalytic polymerizations offer access to special polymer microstructures in aqueous emulsion. However, it must be noted that particularly the expensive rhodium complexes used in the pioneering work display only moderate activities. Latices of butadiene-(CO) polymers suited for a variety of applications are already prepared conveniently on a large scale by established free-radical routes.

5. Vinylic Polymerization of Cyclic Olefins

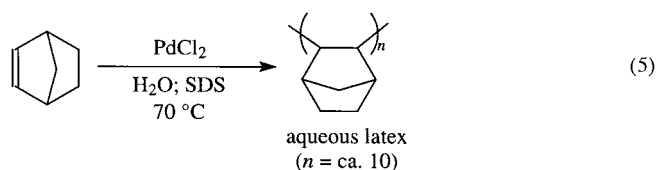
The vinylic polymerization of cyclic olefins, in which the ring structure is left intact, has been less thoroughly investigated than ROMP (see Section 6). An early example of an aqueous polymerization is provided by the rhodium-catalyzed polymerization of cyclobutene in emulsion. Under similar conditions as those described by Rinehart et al. for butadiene polymerization (Section 4), Natta et al. obtained a crystalline, highly stereoregular polymer with low conversions [Eq. (4)].^[113] Ring opening is only a minor side reaction compared with ruthenium-catalyzed aqueous ROMP of cyclobutene (Section 6).



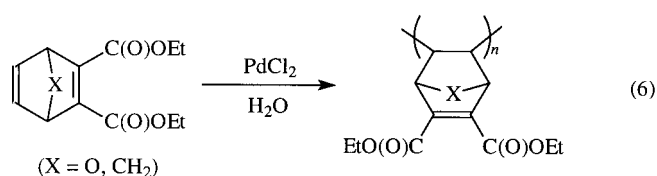
Vinylc polymerization of norbornene (the most common monomer) can be catalyzed in non-aqueous media by complexes of various metals such as titanium,^[114] zirconium,^[115] chromium,^[116] cobalt,^[117] nickel(II),^[118, 119] or palladium(II).^[120–123] Late transition metals can display high activities when, for example, well-defined weakly coordinated nickel(II) complexes^[118] are used as catalyst precursors or with methylaluminumoxane (MAO)-activated nickel(II) and palladium(II) catalysts.^[124–126] The resulting polynorbornenes are amorphous hydrocarbon materials of varying tacticity (depending on the catalyst). They can display high thermal stability and a low dielectric constant. Polynorbornene and functionalized derivatives have been marketed under the brand-name Avatrel as materials for electronics applications.^[127, 128]

It should be noted, that the reactivity of 2,3-substituted norbornenes, which are often employed as monomers in aqueous polymerizations, can be strongly affected by its configuration (*exolendo*). The configuration of the monomers utilized has not always been specified in the literature, which can complicate a detailed comparison of results by different authors. Also, it must be noted that characterization of unfunctionalized polynorbornene obtained with palladium catalysts is often complicated by its notorious insolubility in organic solvents.^[129] The tolerance of norbornene polymerization with $[\text{Pd}(\text{NCCCH}_3)_4](\text{BF}_4)_2$ as an initiator towards added amounts of water (1000 equivalents with respect to Pd) has been described by Mehler and Risse.^[122]

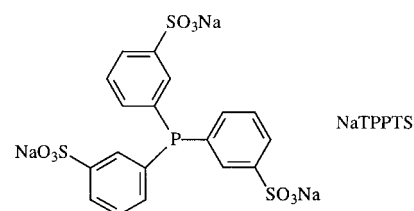
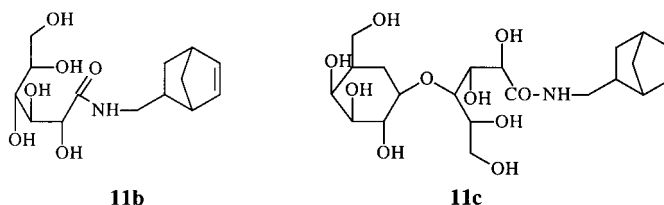
A polymerization of norbornene affording an aqueous latex was reported in 1993 by Perez and co-workers. Norbornene ($T_m = 44^\circ\text{C}$) was treated in aqueous emulsion at 70°C with SDS as an emulsifier and PdCl_2 as a catalyst precursor [Eq. (5)].^[130, 131] With moderate catalyst activities of 70 TO h^{-1} ,



a stable latex consisting of low molecular weight oligomeric material ($\text{DP}_n \approx 10$, DP_n = degree of polymerization) was obtained. Interestingly, very small latex particles of 10 to 20 nm diameter were reported. In well-known free-radical polymerization of olefinic monomers, such small particles are only obtained by microemulsion polymerization. PdCl_2 is slightly water-soluble, and the authors have reasoned that polymerization occurs preferentially at the interface between the water and monomer droplets (although the catalytically active species has not been identified unambiguously). At the same time, Safir and Novak reported the polymerization of polar substituted norbornadienes **11** in aqueous emulsion with PdCl_2 [Eq. (6)].^[132]

**11a**

A few years later Perez and co-workers polymerized a water-soluble norborn-5-en-2-yl-substituted gluconamide (**11b**) and a lactbionamide (**11c**) with water-soluble



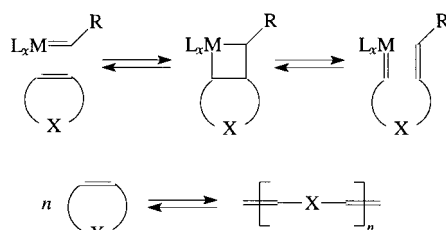
$[\text{PdCl}_2(\text{NaTPPTS})_2]$ in aqueous solution.^[133] Oligomers with a degree of polymerization $\text{DP} = 17$ and 12, respectively, were obtained in a vinylc polymerization with moderate efficiency (86 TO during an entire polymerization run). The water-soluble oligomers form aggregates in solution. Like their analogues formed by ROMP, such glycopolymers have been suggested as therapeutic agents. A cationic polyelectrolyte with a degree of polymerization DP of 94 was obtained by polymerization of [5-(methyleammonium)norborn-2-ene] chloride with PdCl_2 in aqueous solution. Cell transfection by DNA complexes of this polyelectrolyte has been investigated.^[134]

Polymerization of butylnorbornene by a catalyst system containing one equivalent of the water-soluble phosphane ligand NaTPPTS, $[\{(\text{allyl})\text{Pd}(\mu\text{-Cl})_2\}_2]/\text{NaTPPTS}/\text{Li}[\text{B}(\text{C}_6\text{F}_5)_4]$, has also been described. A high activity of $4.5 \times 10^4 \text{ TO h}^{-1}$ has been claimed for this aqueous suspension-type polymerization in a patent.^[135] This may be taken as an indication that substantially higher productivities can be achieved in vinylc aqueous polymerization of norbornene monomers compared to the moderate efficiencies reported to date.

6. Ring-Opening Metathesis Polymerization

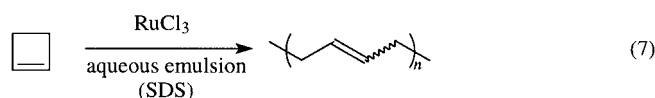
Ring-opening metathesis polymerization (ROMP) of cyclic olefins can be carried out with a variety of catalysts based on different metals,^[136, 137] with molybdenum, tungsten, and ruthenium catalysts being employed most often. In regard to the mechanism of olefin metathesis,^[138] it is generally agreed

upon that metal alkylidenes represent the active species (Scheme 6). Polymers prepared by (non-aqueous) ROMP of olefinic monomers such as norbornene, dicyclopentadiene, and cyclooctene are applied commercially.^[139] In most commercial processes, and also in much academic research, poorly defined in situ catalysts have been applied. The advent of catalytically active metal alkylidenes as well-defined precursors in the 1980s was a strong thrust for the metathesis of olefins as a synthetic method in general, and for aqueous ROMP in particular.^[136, 140–143]



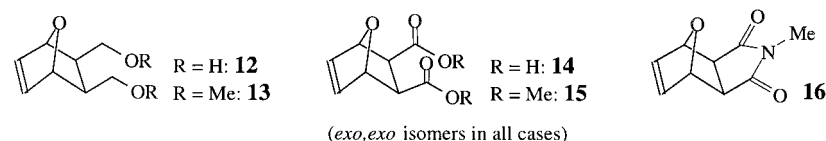
Scheme 6. Mechanism (top) and overall reaction (bottom) of chain growth in ROMP.

An early example of aqueous ROMP was provided by Natta et al. with polymerization of cyclobutene and 3-methylcyclobutene using RuCl_3 as a catalyst precursor.^[144] Low molecular weight stereo-irregular oils were formed with low activities of about 15 TO. Polymerization occurs exclusively by ring opening [Eq. (7)].



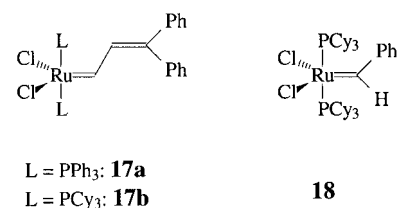
Rinehart et al. have reported ROMP of norbornene and of 2-functionalized norborn-5-enes with polar ester moieties in aqueous emulsion with moderate activities. Iridium(III) or iridium(IV) salts in combination with a reducing agent, or Ir^{I} -olefin complexes were employed as catalyst precursors. Norbornadiene and dicyclopentadiene were also polymerized, with only one double bond reacting.^[101, 145]

In 1988, Grubbs and Novak reported ROMP of aqueous solutions of functionalized 7-oxanorbornenes **12** and **13** using RuCl_3 or $[\text{Ru}^{\text{II}}(\text{OH}_2)_6](\text{OTs})_2$ (OTs = toluene-4-sulfonate) as catalyst precursors.^[146] Polymer molecular weights were found to be higher at more narrow molecular weight distributions ($M_w = 1.3 \times 10^6 \text{ g mol}^{-1}$; M_w/M_n 1.2 for **13**) than those obtained by polymerization in organic solutions. The high catalyst stability towards water is underlined by the possibility of multiple recycling of the catalyst solutions. Advantageously, an initiation period of the catalyst prior to the onset of polymerization is reduced in the presence of water. An analysis by Feast and Harrison of the polymers resulting from



aqueous ROMP of **13** with RuCl_3 and OsCl_3 revealed these materials to be atactic with a varying ratio of *cis* to *trans* double bonds in the backbone.^[147, 148] As a general feature, *trans* linkages are usually obtained preferentially in ROMP of norbornene using RuCl_3 as a catalyst precursor. A number of other functionalized norbornenes (**14–16**) have been polymerized to high molecular weight polymer in aqueous media.^[149–152] Although this issue was only mentioned as an aside, probably in all these cases the catalyst precursor and the monomer (**12–16**) initially formed a homogeneous solution, and the water-insoluble polymer precipitated during the polymerization reaction when a largely aqueous reaction medium was employed. Acyclic olefins can function as chain-transfer agents to regulate molecular weights.^[147, 149, 153] The analysis of the resulting oligomeric products supported the presence of ruthenium alkylidene species.^[153] Also in accordance with intermediacy of a ruthenium alkylidene species in the aqueous polymerization, the addition of ethyl diazoacetate as a carbene source to $[\text{Ru}^{\text{II}}(\text{OH}_2)_6](\text{OTs})_2$ enabled ROMP of less reactive low-strain cyclic olefins such as cyclooctene.^[154]

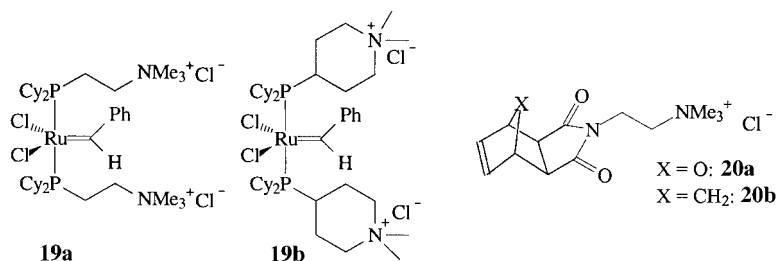
A significant advance was achieved by the utilization of isolated ruthenium carbene complexes as catalyst precursors. Solutions of complex **17a** in organic media were found to be stable to added amounts of water, thus indicating that such



alkylidenes were suitable as catalyst precursors for aqueous reactions.^[155] In subsequent work, rather than the vinyl-substituted carbenes of type **17**, carbene complexes of type **18** were employed most often. They are easily accessible by employing diazoalkanes as the reagents for the generation of the metal-alkylidene moiety and they represent more efficient initiators.^[156, 157] Complexes of the bulky trialkylphosphane PCy_3 (Cy = cyclohexyl) were found to generally display higher activities in ROMP than their PPh_3 analogues. Compounds **17b** and **18** are now available commercially.

As a result of the water-insolubility of these metal carbenes, aqueous polymerizations represent heterogeneous multiphase mixtures. Investigation of ROMP of the hydrophilic monomer **16** or of a hydrophobic norbornene in aqueous emulsion (catalyst precursor **17b** or **18** added as a solution in dichloromethane) or suspension demonstrated that the polymerization can occur in a living fashion. For example, at a monomer to initiator ratio **16/18** = 100/1 with 78% yield of poly-**16** with M_w/M_n 1.07 (versus polystyrene standards) was obtained.^[158] The cationic dodecyltrimethylammonium bromide (DTAB) was used preferentially as a surfactant for polymerization in emulsion. Block copolymers of narrow molecular weight distribution are

also accessible. Living polymerization can be carried out in aqueous solution, without the addition of surfactants or organic cosolvents, by using water-soluble carbene complexes of type **19** and water-soluble monomers **20**.^[159] Interestingly, addition of small amounts of acid (up to 1 equiv DCl) is advantageous for catalyst performance. One reason is that

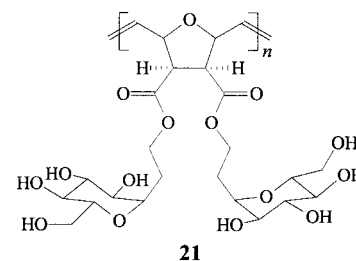


small amounts of hydroxide ions, detrimental for catalyst stability, are eliminated. The acid was found to react with complex **19a** to afford a monophosphane complex and the phosphonium salt of the ligand, which means that remarkably the metal–alkylidene moiety does not react with the acid. The high stability of ruthenium–alkylidene species towards water during the polymerization reaction was confirmed by NMR spectroscopic analysis.

ROMP of norbornene in aqueous emulsion by employing ruthenium(IV) complexes^[160] with bis(allyl) ligands such as the water-soluble $[(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\text{Ru}(\text{OH})_2(\text{OAc})]\text{BF}_4$ as catalyst precursors has been reported by Wache.^[161] High molecular weight polymer with an unusually high *cis* content was obtained with rates of 100 TOh⁻¹. ROMP of deltacyclene, a more peculiar monomer, by RuCl₃ in aqueous suspension has been reported to afford high molecular weight stereo-irregular polymer.^[162]

The synthesis of neoglycopolymers by ROMP has been investigated extensively by Kiessling et al. (the term neoglycopolymer refers to a synthetic, non-natural polymer bearing carbohydrate moieties).^[163] In comparison to other synthetic methods, ROMP can offer the potential for good functional group tolerance together with the possibility of molecular weight control. Carbohydrate-substituted monomers can be employed without protection of the hydroxy groups, thus reducing the synthetic effort and also preventing problems frequently encountered in deprotection steps. As the monomers and also the desired polymers are highly hydrophilic and water soluble, aqueous ROMP can offer the advantage of a homogeneous reaction, which is beneficial for molecular weight control and catalyst efficiency. ROMP of 7-oxanorbornenes substituted with glucose or mannose moieties bound through C– or O–glycosidic linkages afforded neoglycopolymers, such as **21**.^[164, 165]

The reaction can be performed using an aqueous solution of RuCl₃ and monomer to afford the water-soluble polymers. Relative molecular weights of about 10⁶ (by comparison to dextran standards) were estimated. The polymers contain *cis* as well as *trans* double bonds in roughly equal amounts in the backbone which can be reduced to yield a saturated polymer by employing hydrazine reduction.^[165] Utilization of alkyl-



dene complexes **17** or **18** as well-defined catalyst precursors for the polymerization of norbornene derivatives with unprotected carbohydrate residues is again complicated by the water-insolubility of these ruthenium carbenes. Polymerization can be carried out in emulsion (water/dichloromethane/surfactant).^[166, 167] In ROMP of a carboximide-functionalized norbornene (see **16**) N-substituted with a carbohydrate

moiety, increasing average degrees of polymerization in the range of DP_n = 10 to 143 were observed with increasing monomer to catalyst ratio (**18** as a catalyst precursor). This observation indicates a certain degree of control over the molecular weight, although molecular weight distributions were not reported.^[167] The erythrocyte-agglutinating activity of the protein concanavalin A can be inhibited by the binding of carbohydrates. Structure/activity relationship have been investigated using the carbohydrate-substituted ROMP polymers with systematically varied structures as multivalent inhibitors.^[164–166, 168]

It should be noted that removal of metal residues from the unsaturated polymers generated by ROMP is a ubiquitous issue,^[165, 169] as noted early on by Natta.^[144] The introduction of polar moieties, such as hydroxy groups, can be expected to further increase the difficulties of metal removal. A resulting poor oxidative stability can be disadvantageous. Low metal contents are also crucial for meaningful biomedical studies and for potential biological applications. Although challenging, this problem can apparently be solved but detailed published data is currently still limited.^[170, 171]

In the aforementioned ROMPS in aqueous emulsion, the synthesis of polymer latices has been mentioned very briefly in some cases without further discussion of the latex properties. ROMP of the functionalized monomer **13** by RuCl₃ to form stable dispersions of high molecular weight polymer (10⁵ g mol⁻¹ versus polystyrene standards) stabilized by a PEO-*b*-PPO-*b*-PEO (PEO = polyethylene oxide, PPO = polypropylene oxide) triblock copolymer has been reported by Booth and co-workers.^[172] Whereas the monomer is water-soluble, the polymeric product is not, and in this respect the reaction resembles a dispersion polymerization. The stable latices obtained consist of remarkably small particles of 60 nm diameter, for example. Emulsion polymerization of norbornene by various ruthenium catalysts has recently been investigated in detail by Claverie et al.^[173] Using the water-soluble carbene complex **19b** or an in situ system [RuCl₂-(NaTPPTS)₂]/ethyl diazoacetate as water-soluble catalysts, average activities of up to 10⁴ TOh⁻¹ were observed^[174] at 80 °C (for the structure of the water-soluble phosphane NaTPPTS see Section 5). Polynorbornene latices consisting

of relatively small particles of generally less than 150 nm diameter were obtained. The anionic surfactants SDS or Dowfax3B2^[175] were used, and electrostatically stabilized latices with solids contents of up to 46% were obtained with the latter surfactant. Unlike typical free-radical emulsion polymerizations, the particle number increases continuously with conversion, thus indicating continuous nucleation. The observed dependence of particle numbers on reaction conditions indicates that homogeneous nucleation occurs, even in the presence of surfactant micelles. To enable utilization of the commercially available hydrophobic carbene complex **18** as a catalyst precursor for latex synthesis, the complex was employed as a solution in toluene/hexadecane miniemulsion droplets (see Section 3). Hereby, in addition to norbornene, cyclooctene and cyclooctadiene, which are unreactive towards the water-soluble catalysts, can be polymerized to latices of high molecular weight polymers. Copolymerization of cyclopentene and cyclooctene by **18** in miniemulsion has also been reported independently by Kühn et al.^[179] Copolymerization of norbornene with poly(ethylene oxide)-substituted norbornene macromonomers by **18** to afford latex particles has been reported.^[176] Although this reaction was carried out in ethanol/dichloromethane mixtures and thus does not represent an aqueous polymerization, from the viewpoint of colloid chemistry it is interesting that the concept of polymerizable stabilizers (“surfmers”),^[177] well known from free-radical polymerization, has been applied to a dispersion-type ROMP.

In summary, ruthenium-catalyzed aqueous ROMP has proven to be a versatile method for the preparation of polar substituted polymers. The resulting materials have been utilized for biomedical studies. Utilization of well-defined metal carbenes as initiators enables control over the molecular weight, and water-soluble ruthenium carbenes have recently become available. Monomer/metal ratios on the range of 100/1 have been typically utilized in the polymerization of functionalized norbornenes. Whereas such catalyst or initiator efficiencies are moderate in comparison to other types of aqueous catalytic polymerizations (Sections 2–4),

they are certainly satisfactory as a tool for the preparation of special, for example, biologically active, materials. Polymer latices have been prepared successfully by aqueous ROMP, and the particle formation process has been studied recently.

7. Summary and Outlook

The principal possibility of aqueous catalytic polymerization of olefinic monomers was demonstrated early on, with pioneering work originating from the 1960s. However, since then significant advances have been achieved only in very recent years: 1) the number of polymers prepared in aqueous catalytic polymerizations has grown substantially; 2) the preparation of stable aqueous polymer latices has been investigated; and 3) strong improvements in catalytic activity have been achieved. High molecular weight polymers ranging from amorphous or semicrystalline hydrocarbons to highly polar water-soluble materials are now accessible. The current state of these developments is summarized in Table 1.

What are the driving factors for these ongoing developments? The discovery of new late transition metal based polymerization catalysts and the availability of well-defined catalyst precursors (not requiring water-sensitive alkylaluminum cocatalysts) has certainly contributed. An increased need for environmentally benign processes in general makes water an attractive reaction medium. With polymer latices, this advantage is not restricted to the polymerization process, but also applies to the product itself. In addition to environmental concerns, water is advantageous as a medium for polymerizations since it enables efficient processes to be achieved. In the context of current general interest in the synthesis and properties of micro- and nanoparticles, it can be noted that catalytic polymerization in aqueous emulsion provides convenient access to dispersions of polymer particles in the size range of about 80 nm to 1 μm . Finally, the functional group tolerance of the catalysts has enabled polymerization of special highly polar monomers to afford polymers, for

Table 1. Overview of aqueous catalytic polymerization of olefins.

Reaction type	Examples of catalyst precursors used	Typical activity reported [TO h ⁻¹] ^[a]	Results
alternating olefin – CO copolymerization	cationic Pd ^{II} – diphosphane complexes	6×10^4	semicrystalline ethylene – CO copolymers are accessible with high activities in suspension-type polymerization. Stable latices of 1-olefin copolymers can be obtained
ethylene and 1-olefin polymerization	neutral Ni ^{II} (X --- O) complexes (X = P, N)	2×10^5 (Ni)	stable latices of semicrystalline ethylene homo- and copolymers with high activities amorphous highly branched polyethylene in suspension-type polymerization
	cationic Pd ^{II} – diimine complexes	10^3 (Pd)	
butadiene polymerization	alkylaluminum-activated cobalt catalysts Rh salts	10^3 (Co) 2×10^3 (Rh)	latices of syndiotactic 1,2-polybutadiene (Co)
vinylc polymerization of cycloolefins	Pd ^{II} salts	ca. 10^2	polymerization of norbornene; polymerization of polar-functionalized norbornenes
ROMP	Ru – alkylidene complexes or Ru salts	10^4 (norbornene) 10^2 (functionalized norbornenes)	living polymerization of polar-functionalized norbornenes. Controlled synthesis of polymers for biomedical investigations; latices of norbornene and functionalized derivatives

[a] The activities have been determined under strongly varying conditions, thus they should only be taken as a measure of the order of magnitude. TO (turnovers): substrate converted [mol] per metal used [mol].

example, for biomedical studies. In such small-scale reactions water is a convenient solvent for the polar reactants which enables polymerization in a controlled fashion in homogeneous solution.

What issues can be of interest in the future? As most latices prepared by catalytic polymerization have become available only recently, no data has been published regarding their properties relevant for applications, such as latex stability under different conditions, film formation, and film properties. Co- and terpolymerization of readily available monomers, including polar-functionalized olefins, can be expected to enable control of the latter properties. Particle morphology, for example, the generation of domains of different polarity such as in core-shell particles, represents another interesting aspect. A comprehensive picture remains to be established with regard to the mechanism of particle formation, polymerization kinetics, and, for example, the location of the catalytic centers during the different stages of the reaction (aqueous phase, inside monomer droplets or polymer particles, or on the interface). Further improvements in catalyst performance based on a systematic understanding are certainly also an issue. In a polymerization aimed at preparing a latex, it is desirable to leave the catalyst in the product in order to maintain the intriguing simplicity of this direct route to a polymer dispersion. Thus, catalyst performance must be higher than the levels acceptable in many catalytic synthesis of small molecules ($< 10^3$ TO) where the catalyst is recovered. On the other hand efficiencies must not necessarily compete with Ziegler catalysts or metallocenes ($> 10^7$ TO). Some of the recent discoveries reviewed demonstrate that sufficient catalyst performance can principally be achieved.^[178]

In summary, recent findings have demonstrated aqueous catalytic polymerizations to be a versatile topic. Various potential applications can be envisioned. Equally, a number of attractive subjects for fundamental research in the areas of colloids science, polymer chemistry, coordination chemistry, and catalysis are evident.

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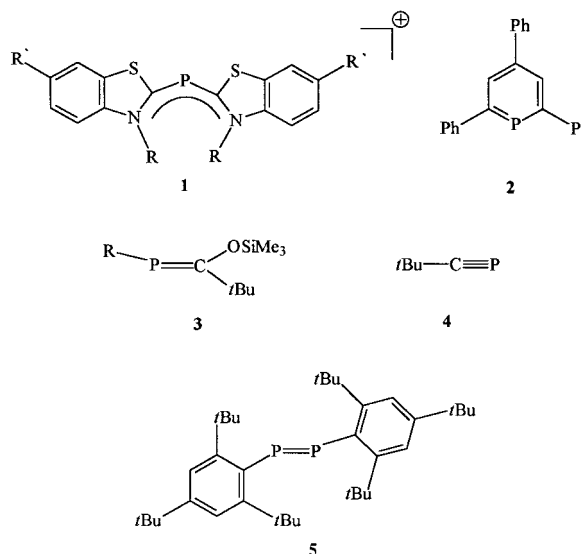
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Phosphorus Heterocycles: From Laboratory Curiosities to Ligands in Highly Efficient Catalysts

Lothar Weber*

Abstract: Phosphabenzene and phosphaferrrocenes were among the first compounds with P–C multiple bonds. For nearly 30 years the chemistry of these molecules was essentially a domain left to basic researchers. Recently, however, it was reported that transition metal complexes with phosphabenzene and phosphaferrrocene ligands exhibit remarkable potential as catalysts. Catalysts based on rhodium (I) and various phosphabenzene appear to be superior to classical systems in the hydroformylation of terminal and internal alkenes. In addition planar-chiral phosphaferrrocene species display an excellent performance as directing ligands in a series of enantioselective asymmetric syntheses.



More than any other element phosphorus plays a key role in the development of modern main group chemistry. The synthesis of the phosphamethyne cyanine cations **1** by Dimroth et al.,^[1] and the first phosphabenzene derivative by Märkl^[2] as well as the discoveries of the first acyclic phosphalkenes **3**^[3] and phosphalkynes **4**^[4] by Becker et al. and the first diphosphenes **5** by Yoshifuji et al.^[5] are landmarks in the chemistry of phosphorus compounds in low coordination.

At first these molecules were regarded as “laboratory curiosities” with an exotic chemistry, which was mainly left to basic researchers and theoreticians.^[6] Recently, however, a remarkable change took place, when it was shown that some of the species under discussion, such as, phosphabenzene and phosphaferrrocenes function as versatile ligands in coordination chemistry. Their excellent π -acceptor properties are in marked contradiction to their nitrogen analogues and to classical tertiary phosphanes and makes them useful as ligands in low-valent and electron-rich transition metal complexes, which are relevant for the homogenous complex catalysis. This minireview provides an overview of the state of the art of

this research area. The material is organized by the type of reaction rather than by the nature of the catalysts and its directing ligand.

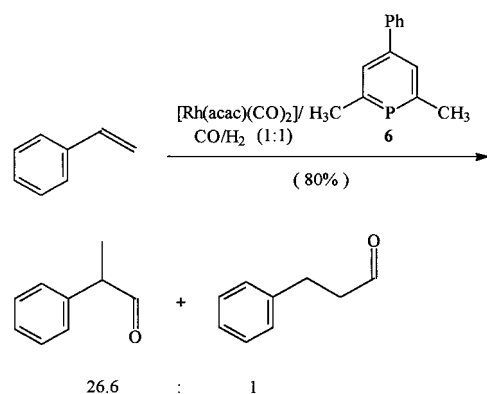
1. Hydroformylations

Since its discovery by Roelen in 1938 hydroformylation has emerged as one of the most important transformations in the field of homogenous complex catalysis.^[7] But even after more than six decades of intense investigations on various aspects of this process, the problem of the simultaneous control of reactivity and selectivity remains challenging. Moreover, the hydroformylation of internal and higher substituted alkenes still awaits a satisfactory solution, which is highly desirable from both its academic interest as well as its industrial importance.

Since their first preparation by Wilkinson and co-workers rhodium–phosphane complexes have played an important role as potent catalysts in hydroformylation.^[8] Intense studies have revealed that this reaction is severely hindered or even completely inhibited by σ -donor ligands, whereas pronounced π -acceptor ligands have provided increased activities and selectivities of the catalysts.^[9–13]

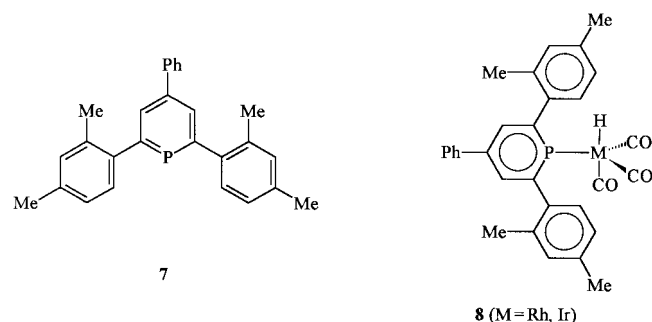
[*] Prof. Dr. L. Weber
Fakultät für Chemie
Universität Bielefeld
Postfach 100131, 33501 Bielefeld (Germany)
Fax: (+49) 521-106-6146
E-mail: lothar.weber@uni-bielefeld.de

Recently, Breit et al. have launched a systematic investigation of the use of phosphabenzene, [2, 4] as directing ligands in hydroformylation catalysts. [15] The π -acceptor capability of phosphabenzene is between that of triphenylphosphane and that of phosphites. In the regioselective hydroformylation of styrene a rhodium catalyst with phosphabenzene **6** as a ligand displayed an activity twice as high as that of the conventional Rh/PPh₃ catalyst used in industry (Scheme 1). Thereby, the selectivity of branched to linear aldehydes is excellent (22.6:1).



Scheme 1. Hydroformylation of styrene; acac = acetylacetonate.

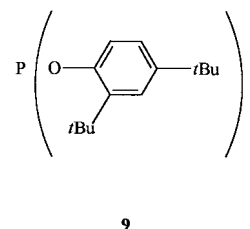
Trigonal-bipyramidal η^1 -phosphabenzene complexes such as **8** were identified as the catalytically active species by NMR spectroscopy studies on mixtures of the rhodium precursor and phosphabenzene **7** under an atmosphere of synthesis gas and a pressure of 4.06×10^4 kPa.



The catalytic performance of the ligand is governed by steric requirements. Thus, the change from the *o,o'*-dimethyl derivative **6** to ligand **7** resulted in a five-fold increase of the reaction rate of the hydroformylation of 1-octene. The reaction was conducted at 90 °C and a pressure of 1×10^3 kPa (CO/H₂ 1:1). After 30 min 78 % of the 1-octene was consumed. In addition to aldehydes internal octenes (20 %) were also formed at this stage. After another 30 min the ratio of these octenes decreased in favor of 2-ethyl heptanal and 2-propyl hexanal. An increase of the temperature to 130 °C and of the gas pressure to 4×10^3 kPa accelerates the turnover frequency (TOF) of the aldehyde formation by a factor of eight. Under these conditions the conversion of 1-octene into aldehydes was completed after 50 min, whereas the hydroformylation of the isomeric octenes took 60 min. This experiment made obvious that compound **7** is also efficient as a

cocatalyst in the hydroformylation of internal and higher substituted alkenes.

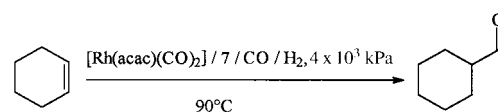
For the hydroformylation of internal olefins the standard Rh/PPh₃ system displays an unsatisfactorily low catalyst activity. Replacement of triphenylphosphane by bulky phosphites such as **9** gave rise to an important improvement in this field. [10, 16] Although the catalytic activity of such systems is extremely high, disadvantages in the use of phosphites are caused by their inherent lability towards hydrolysis and their propensity to undergo degradation reactions.



The hydroformylation of cyclohexene at 90 °C and 2×10^3 kPa was performed as a test reaction with **2** or **9** as modifying ligands.

After 1 h for both systems olefin conversions of around 28 % and TOF of approximately 215 mol catalyst⁻¹ h⁻¹ were obtained. [15b] Here, importantly, the remarkable stability of the phosphabenzene/Rh systems allows the reuse of the catalyst at least two more times in this reaction without loss of its catalytic activity.

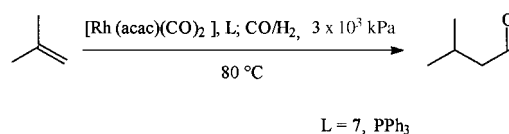
Cyclohexene was converted into cyclohexylcarbaldehyde with a selectivity ≥ 99 % when hydroformylated at 90 °C, under 4×10^3 kPa synthesis gas, and with a catalytic amount of the mixture of [Rh(acac)(CO)₂] and **7** (Scheme 2). First-order kinetics with respect to the alkene agrees with the coordination of the substrate as the rate-determining step of the reaction. [15d]



Scheme 2. Hydroformylation of cyclohexene.

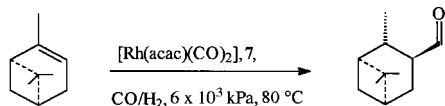
Acyclic internal alkenes such as an *E/Z* mixture of 2-octene (77:23) were also successfully hydroformylated by a catalyst derived from [Rh(acac)(CO)₂] and phosphabenzene **7**. Among the products, 24 % of *n*-nonanal was generated, which indicates that 33 % of the employed 2-octene was isomerized to 1-octene prior to hydroformylation. With the commercial catalyst based upon the Rh/PPh₃ system, 36 % of the octenes resisted hydroformylation, and only 5 % of nonanal was detected.

The superiority of the phosphabenzene/Rh catalyst over the classical Rh/PPh₃ system was also convincingly demonstrated in the hydroformylation of 2-methylpropene, where after 4 h at 80 °C chemo- and regio-selectivities of > 99 % were achieved (Scheme 3).



Scheme 3. Hydroformylation of 2-methylpropene.

Whereas the standard catalyst Rh/PPh_3 completely fails with the hydroformylation of trisubstituted alkenes such as α -pinene, this olefin is smoothly converted in the respective aldehyde with Breit's phosphabenzene Rh /catalyst. Thereby the aldehyde selectivity is $\geq 99\%$ whereas regio- and diastereo-selectivities $\geq 90\%$ were determined (Scheme 4).

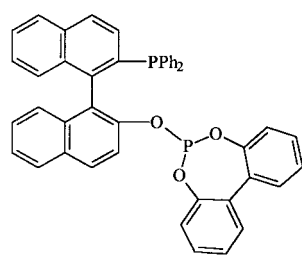


Scheme 4. Hydroformylation of α -pinene.

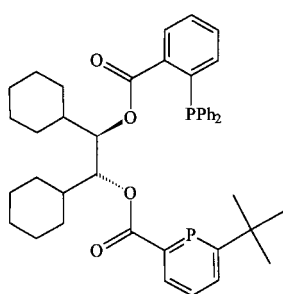
Tetramethylethylene cleanly reacts with synthesis gas at 100°C and 6×10^3 kPa catalyzed by the Rh catalyst discussed here, with **7** as directing ligand to afford 3,4-dimethylpentanal, which implies an alkene isomerization prior to a regioselective hydroformylation process.^[15d]

To date BINAPHOS **10** from Takaya and co-workers has proven to be the most selective modifying ligand in hydroformylation reactions. This bidentate chelating ligand is characterized by two donor sites which differ essentially in their σ -donor/ π -acceptor capabilities.^[17] It was clear that the catalytic performance of 2,6-disubstituted phosphabenzene could be enhanced by the introduction of a second donor site with different ligating properties as illustrated in **11–13**.

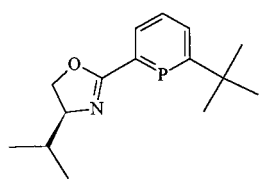
Compounds **11–13** were combined in a ratio of 2:1 with $[\text{Rh}(\text{acac})(\text{CO})_2]$ in toluene and these systems were then used as catalysts in the hydroformylation of styrene (20°C , 5×10^3 kPa H_2/CO). The reaction was stopped after 22 h. The catalyst system generated with **11** as the modifying ligand gives a conversion of 42% and a good regioselectivity (2-phenylpropanal:3-phenylpropanal 21.4:1).



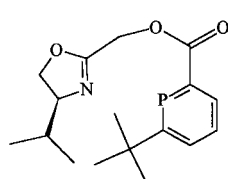
(*R,S*)-binaphos **10**



11



12

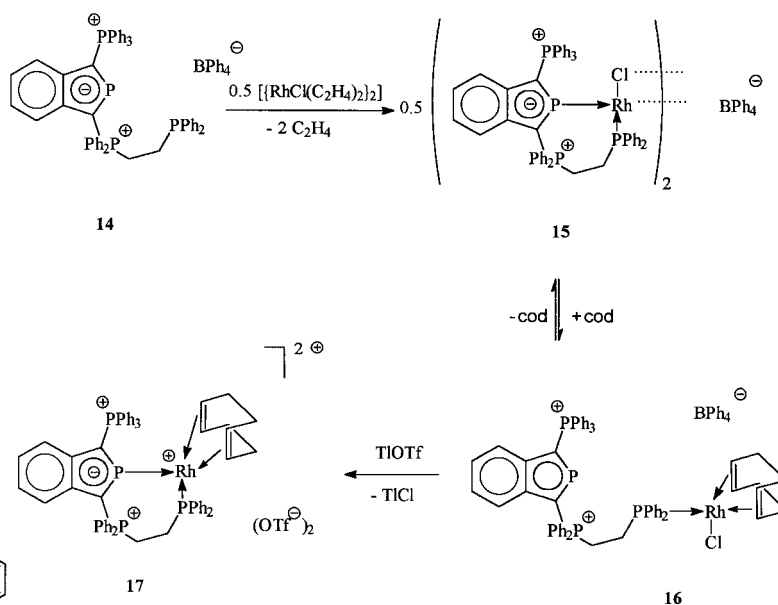


13

Significantly improved conversions (98%) with comparable regioselectivities were achieved with **13** as a ligand. In contrast to this the employment of **6** as the directing ligand only led to a 5% conversion and the exclusive production of 2-phenyl propanal.^[15a]

During the course of an investigation on the coordinating properties of the bisphosphonio benzophospholide cation **14** a series of rhodium complexes was synthesized and subsequently employed as potential catalysts in hydroformylation reactions.^[18]

Hydroformylation of 1-hexene at 20°C and 4×10^3 kPa of synthesis gas in the presence of catalytic amounts of complexes **15** and **17**, gave conversions of 85% and 27%, respectively, with turnover number (TON) of 850 or 270 mol aldehyde/mol catalyst⁻¹ after 24 h. The activity of catalyst **15** was estimated to be superior to that of the standard system $[\text{Rh}(\text{acac})(\text{CO})_2]/\text{PPh}_3$ and well comparable to Breit's phosphabenzene/ Rh catalysts (Scheme 5). However, the ratio of linear to branched aldehydes of 1.6:1 and 2.7:1 with catalysts **15** and **17**, respectively, is still unsatisfactory.

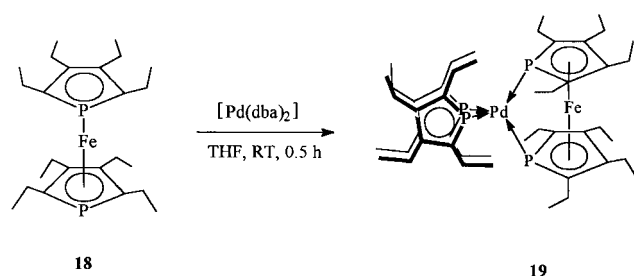


Scheme 5. Synthesis of benzophospholide– Rh complexes; cod = (*Z,Z*)-1,5-cyclooctadiene, OTf = trifluoromethanesulfonate (triflate).

2. Coupling Reactions

2.1 Suzuki Coupling

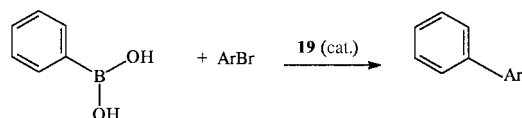
In transition metal complexes, 1,1-diphosphaferrocenes may function as chelating or as bridging ligands. Both modes of coordination are realized in palladium complexes, which turned out to be excellent catalysts in coupling processes. The treatment of bis(dibenzylidene acetone) palladium(0) with two molar equivalents of the octaethyl diphosphaferrocene **18** led to the formation of complex **19** (Scheme 6). According to an X-ray structural analysis the Pd atom of **19** has a nearly tetrahedral geometry. The Pd–P bond lengths are long (2.3815(6) and 2.3852(6) Å), which is rationalized by the



Scheme 6. Synthesis of **19**; dba = *trans,trans*-dibenzylidene acetone.

spherical character of the lone pair of electrons (3s) at the phosphorus atoms. Consistently, the hemilabile ligand **18** is quantitatively displaced by the bidentate diphosphanes $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2$ ($n = 2,3$) under mild conditions.^[19]

Compound **19** proved to be a very efficient catalyst in the Suzuki coupling between phenylboronic acid and various aryl bromides in boiling toluene and in the presence of K_2CO_3 as a base (Scheme 7). The reaction of the boronic acid and



Ar = 4-MeC(O)C₆H₄; 3-thienyl, 2-MeOC₆H₄, Ph

Scheme 7. Suzuki coupling with **19** as catalyst.

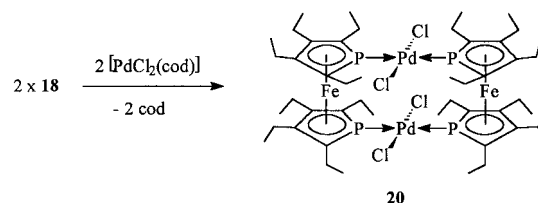
4-bromoacetophenone in the presence of 1×10^{-4} mol % of catalyst furnished a conversion of 77 % and a TON of 7.7×10^5 mol product mol Pd⁻¹ after 1 h. After 20 h the conversion was quantitative (TON = 9.8×10^5). Very good results were also obtained in the Suzuki coupling of 3-thienyl bromide, 2-methoxyphenyl bromide, and phenyl bromide. Here, however, 5×10^{-3} mol % of catalyst was necessary and after 1 h lower TONs (13 400–16 000) were observed.

The catalyst activity of compound **19** clearly does not attain that of Buchwald's catalyst derived from (*o*-di-*tert*-butylphosphanyl)biphenyl and $\text{Pd}(\text{OAc})_2$ (TON = 9.1×10^7 , 24 h heating).^[20] The catalytic performance of **19**, however, is comparable to the second best catalyst for the Suzuki coupling which is an *ortho*-palladated tris(2,4-di-*tert*-butylphenyl)phosphite (TON = 8.7×10^5 , 1 h).^[21]

2.2 Miyaura Coupling

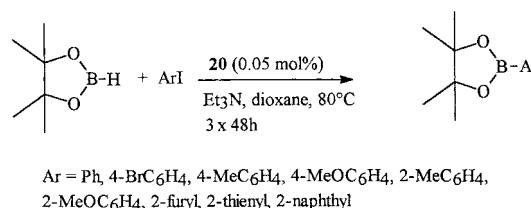
Classical syntheses of boronic esters are based upon reaction of Grignard reagents or organolithium reagents with boron compounds. Usually base-sensitive functionalities are not tolerated in these transformations. The Pd-catalyzed cross-coupling reaction involving the condensation of either tetraalkoxydiboranes(4) or dialkoxyboron hydrides with aryl halides provides an alternative access to boronic esters.^[22] This process, known as the Miyaura coupling, requires relatively large amounts of catalyst (1–5 mol %) and improvements aimed at reducing the load of catalyst would improve this reaction.

The dimeric Pd^{II} complex **20** resulted from the combination of equimolar amounts of diphosphaferrocene **18** and $[\text{Pd}(\text{cod})\text{Cl}_2]$ (Scheme 8). With only 0.05 mol % of catalyst **20** the Miyaura coupling between aryl iodides and 1.5 equivalents of pinacolborane, carried out in the presence of



Scheme 8. Synthesis of **20**.

3 equivalents of triethylamine, lead to a quantitative conversion. The reaction took 48 h in dioxane at 80 °C, and most importantly, three consecutive batches could be run without significant decrease in yield and TOF. Excellent yields (86–98 %) and TON up to 2966 mol product mol Pd⁻¹ exceed classical catalysts by two orders of magnitude and impressively underline the catalytic activity of **20** (Scheme 9). It was assumed that the reactive species in this coupling is an (octaethyldiphosphaferrocene)Pd(0) complex containing 12 or 14 valence electrons, which is derived from **20** by ligand dissociation and reduction.^[23]



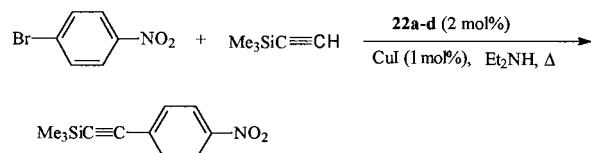
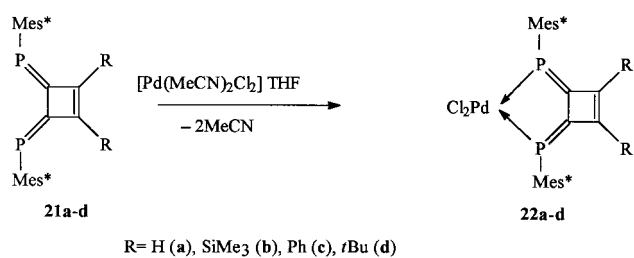
Scheme 9. Miyaura coupling with **20** as catalyst.

2.3 Sonogashira Coupling

Yoshifuji and co-workers synthesized the dichloropalladium(II) complexes **22a–d** from the bulky diphosphinidene cyclobutane ligands **21a–d** and $[(\text{MeCN})_2\text{PdCl}_2]$, and then explored their applicability in the Sonogashira coupling between *p*-bromonitrobenzene and trimethylsilylacetylene^[24] (Scheme 10). The coupling product was formed in yields of up to 77 % over 2–7 h in refluxing diethylamine. When the reaction was performed at ambient temperature the yield was low (10 %), this is not the case with $[\text{PdCl}_2(\text{PPh}_3)_2]$ as the catalyst which affords *p*-nitro(trimethylsilyl)ethynylbenzene in 91 % yield after 4 h.^[24]

3. Asymmetric Syntheses

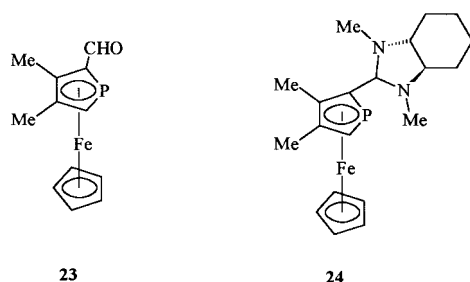
Chirality that results from π complexation of a prochiral ligand to a metal center is commonly referred to as “planar chirality”. If the respective π ligand is a ring system with one



Scheme 10. Syntheses of **22a–d** and Sonigashira coupling; Mes* = 2,4,6-tri-*tert*-butylphenyl.

or more donor atoms such planar-chiral heterocycles could be promising catalysts in asymmetric synthesis.^[25]

The first planar-chiral chelate ligands derived from a phosphaferrrocene skeleton were recently designed in the groups of Ganter^[26] and Fu.^[27] The key step in Ganter's work concerned the resolution of the enantiomeric aldehydes **23** by the separation of the diastereomeric amins **24** by column

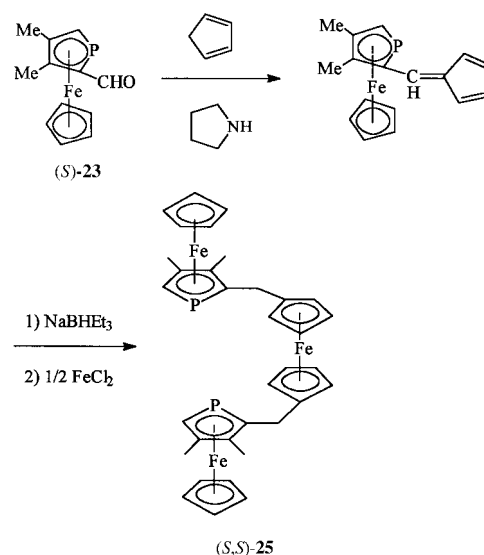


chromatography. The pure enantiomer (*S*)-**23** was converted in a three-step reaction into the enantiomerically pure 1,1-bis(phosphaferrrocenyl)ferrocene (*S,S*)-**25**^[26c] (Scheme 11).

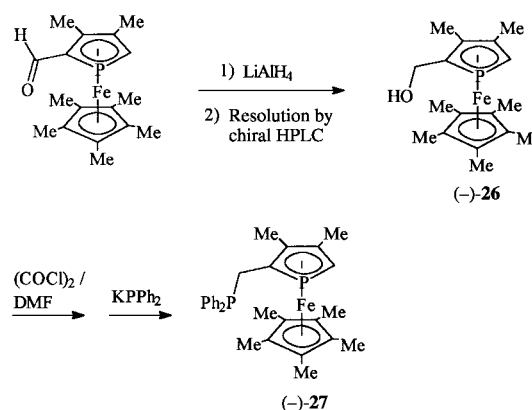
Fu and Qiao synthesized the chiral 2-phosphanylmethyl-phosphaferrrocene **27** from the enantiomerically pure alcohol (–)-**26** by chlorination and subsequent nucleophilic Cl/PPh₂ exchange. The preceding resolution of racemic **26** was accomplished by chiral HPLC (Scheme 12).^[27]

3.1 Hydrogenation Reactions

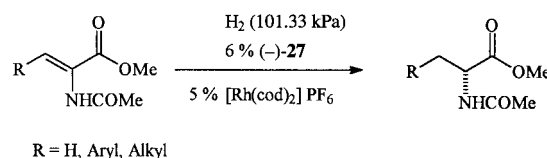
The planar-chiral ligand (–)-**27** was combined with [Rh(cod)₂]₂PF₆ to afford an effective catalyst for the asymmetric hydrogenation of methyldehydroaminocarboxylates in ethanol to the respective esters of the amino acids. Yields of 92–100% and enantiomeric excesses of 79–96% were obtained (Scheme 13).^[27]



Scheme 11. Synthesis of (*S,S*)-**25**.



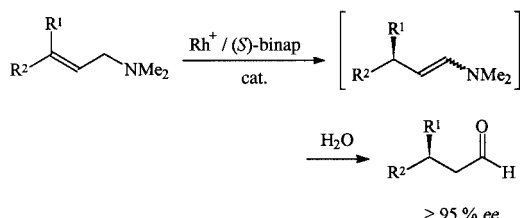
Scheme 12. Synthesis of (–)-**27**.



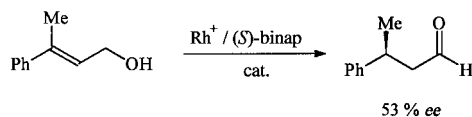
Scheme 13. Asymmetric hydrogenation of protected methyldehydroaminocarboxylates with a Rh/(–)-**27** catalyst.

3.2 Enantioselective Isomerization of Allylic Alcohols to Aldehydes

The highly enantioselective isomerization of allylic amines to enamines, catalyzed by a Rh⁺/BINAP complex represents one of the most remarkable achievements in the area of asymmetric catalysis (Scheme 14).^[28] Comparable success has not been accomplished for the corresponding allylic alcohols despite the obvious usefulness of this transformation. The isomerization of 3-methyl cinnamic alcohol by means of the Rh⁺/(*S*)-BINAP catalyst furnished 3-phenylbutanal in modest yields (47%) with an *ee* value of only 53% (Scheme 15).^[29] Considerable progress in the asymmetric isomerization of (*Z*)-configured allylic alcohols to aldehydes was achieved by

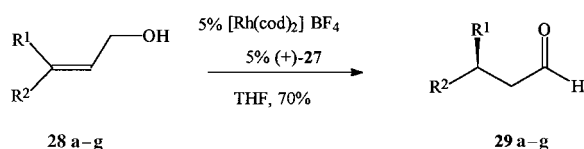


Scheme 14. Enantioselective isomerization of allylic amines and subsequent hydrolysis to aldehydes.



Scheme 15. Isomerization of 3-methylcinnamic alcohol by Rh^+/binap catalysis.

Fu and co-workers when a catalyst based upon planar-chiral phosphaferrrocene (+)-**27** and $[\text{Rh}(\text{cod})_2]\text{BF}_4$ was employed. Enantioselectivities of 64–86% and improved yields (55–91%) were observed (Scheme 16).^[30] The formation of aldehyde **29 g** (Table 1) indicates that for the success of this reaction the presence of aryl substituents at the carbon–carbon double bond of the allylic alcohol is not required.

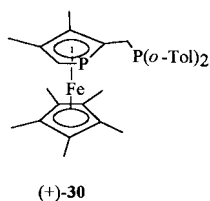


Scheme 16. Enantioselective isomerization of (Z)-allylic alcohols **28** by catalysis with $\text{Rh}^+/(+)\text{-27}$.

Table 1. Yield and enantioselectivity in the isomerization of (Z)-allylic alcohols **28**, catalyzed by $\text{Rh}^+/(+)\text{-27}$.

28/29	R ¹	R ²	Yield [%]	ee [%]
a	Ph	Me	55	64
b	Ph	<i>i</i> Pr	91	83
c	<i>i</i> Pr	Ph	81	78
d	4-ClC ₆ H ₄	<i>i</i> Pr	74	86
e	4-MeC ₆ H ₄	<i>i</i> Pr	64	80
f	4-MeOC ₆ H ₄	<i>i</i> Pr	87	82
g	<i>c</i> -C ₆ H ₁₁	Me	75	72

At this point it should be noted that the complex which results from the combination of $[\text{Rh}(\text{cod})_2]^+$ and phosphaferrrocene (**27**) is a precatalyst, which is hydrogenated an hour before use to completely remove 1,5-cyclooctadiene as cyclooctane. The catalyst activity and enantioselectivity could be further improved by the replacement of the diphenylphosphanylmethyl group in ligand **27** by the sterically more demanding di-*o*-tolylphosphinomethyl function to give **30**. The improvement of the enantioselectivity by the use of (+)-**30** instead of (+)-**27** in the precatalyst was illustrated in the isomerization of **28 c** to give **29 c** (cf. Table 1, row 3). The yield



increased from 81 to 95% and the *ee* values from 78 to 82%.^[31]

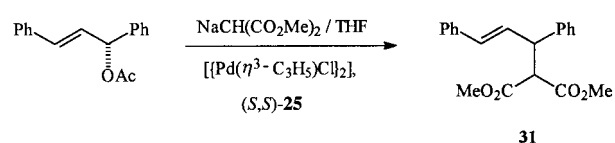
A further enhancement of the *ee* value to 93% was realized by running the reaction at 100 °C and by the direct use of $[\text{Rh}(\text{cod})((+)\text{-30})]\text{BF}_4$. This complex effects isomerization without the need to first hydrogenate the cyclooctadiene. In general these complexes are highly suitable as catalysts for the asymmetric isomerization of whole series of allylic alcohols, in yields that are 3–26% higher. By way of comparison, the enantiomeric excess achieved for the (*E*)-allylic alcohols are superior to those observed for the *Z*-isomers by 7–19%.

The isomerization can also be performed on a preparative scale (ca. 1 g) employing 1 mol% of catalyst without significant loss in yield or enantioselectivity. It is worth mentioning that the catalyst for these enantioselective isomerizations can be re-used. Thus $[\text{Rh}(\text{cod})((-)\text{-30})]\text{BF}_4$ was crystallized directly from the reaction mixture by adding pentane (68% yield) and used for the isomerization of **28 c** without any loss in yield or enantioselectivity.

Mechanistic work has established that these asymmetric isomerizations proceed through an intramolecular 1,3-hydrogen migration pathway and that the chiral catalyst preferentially activates one of the enantiotopic hydrogen atoms of the CH_2OH function.^[31]

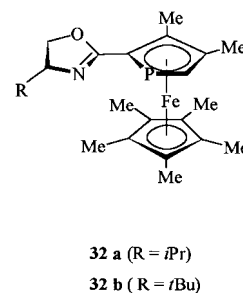
3.3 Allylic Alkylations

The efficiency of phosphaferrrocenes as chiral modifying ligands in asymmetric synthesis was also explored in the Pd-mediated enantioselective allylic alkylation reactions.^[32] The asymmetric allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate with sodium dimethylmalonate was achieved with a catalyst prepared by combination of 1% $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$ and 2% of the chiral ligand (*S,S*)-**25**. Product **31** was formed in 78% yield with an enantiomeric excess of 79% (Scheme 17).^[26c]



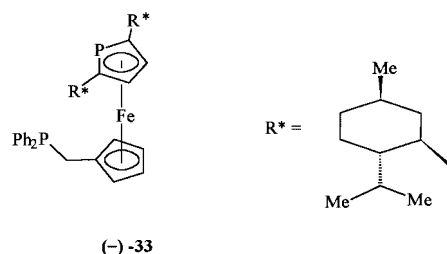
Scheme 17. Allylic alkylation of 1,3-diphenyl-2-propenylacetate with $\text{NaCH}(\text{CO}_2\text{Me})_2$ catalyzed by (*S,S*)-**25**.

A comparable stereoselectivity of (*S*)-**31** (79 and 82% *ee*, respectively) with considerably improved chemical yields (92 and 94%, respectively) were achieved when the Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate was performed with dimethyl malonate and the planar-chiral phosphaferrrocenyl oxazolines **32 a** and **32 b** as ligands. Thus, it was demonstrated that the stereocontrol was provided by the planar-chirality of the com-

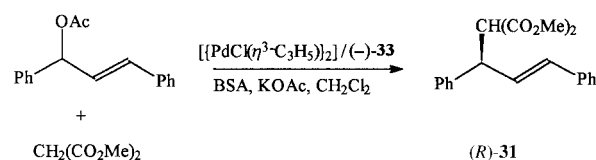


plex rather than by the chirality of the oxazoline substituent.^[33]

Recently, Hayashi et al. reported the synthesis of the novel phosphanylphosphaferrocene (–)-**33**. The basic framework of chiral (–)-**33** is different from that of the planar-chiral phosphapherrocenes **25** and **27** of the Ganter and Fu groups, as the chirality in (–)-**33** is introduced into the complex by an enantiomerically pure chiral phospholide with menthyl substituents in the 2,5-positions.^[34]



Combination of phosphapherrocene (–)-**33** and $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)_2]$ furnished a catalytically active complex which was utilized in situ for the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of bis(trimethylsilyl)acetamide (BSA). Quantitative formation of (*R*)-**31** was complete after 24 h. The enantioselectivity of this transformation sensitively depended on the molar ratio of ligand (–)-**33** to palladium. An enantiomeric excess of 97% is realized with a ligand:Pd ratio of 1.5:1. An increase of this ratio is accompanied by a decrease of stereocontrol. On the other hand the employment of a ratio ligand:Pd of 0.75:1 leads to an *ee* value of 98%. The reaction was slower when carried out at –20 °C, after 96 h a chemical yield of 59% and an enantioselectivity of 99% was achieved, which is one of the highest values reported to date for this reaction (scheme 18). The correlation between the



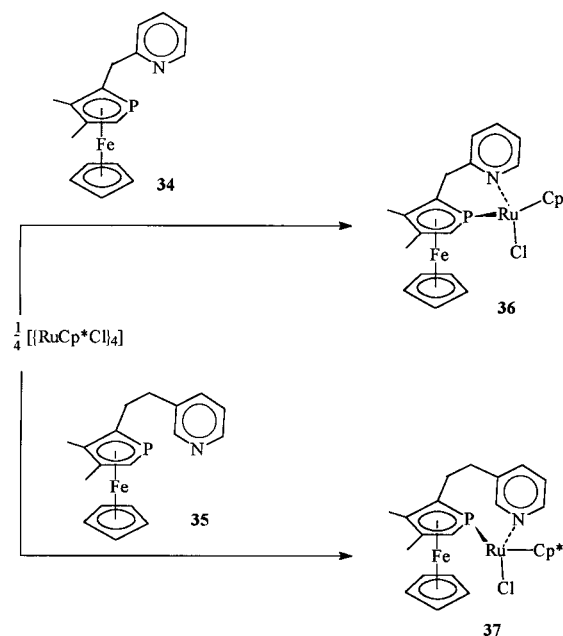
Scheme 18. Allylic alkylation of 1,3-diphenyl-2-propenylacetate with $\text{CH}_2(\text{CO}_2\text{Me})_2$ by catalysis with (–)-**33**.

(–)-**33**:Pd molar ratio and the enantioselectivity in the Pd-catalyzed allylic alkylation can be rationalized by different modes of ligand coordination, a monodentate ligation by the Ph_2P unit and a bidentate, chelating fashion through both P-atoms are conceivable. Only with the latter mode of coordination, which dominates at a stoichiometry ligand:Pd $\approx$ 1:1, is a significant optical induction feasible.^[34]

3.4 Diastereoselective Complex Formation

In the coordination chemistry of transition metals there are numerous ligands, the chirality of which results from the presence of asymmetrically substituted centers. In contrast to this, bidentate chelating ligands with planar-chirality derived

from π -coordination of heterocycles are to date limited to a few examples. In Section 3.2 complex $[\text{Rh}(\text{cod})(\text{27})]\text{PF}_6$ was discussed in this context. Basically, it should be possible to diastereoselectively induce the formation of a stereogenic center at a metal atom by the coordination of a bidentate planar-chiral ligand. In keeping with this, treatment of $[\{\text{RuCp}^*\text{Cl}\}_4]$ ($\text{Cp}^* = \text{C}_5\text{Me}_5$) with the pyridyl-functionalized phosphapherrocenes **34** and **35** stereoselectively furnished the chelate complexes **36** and **37** with diastereomeric ratios of d.r. $>99:1$ and $95:5$, respectively (Scheme 19).^[26d] The high diastereoselectivity observed is in sharp contrast to work of Consiglio et al. who obtained 1:1 mixtures of diastereomers from the reaction of $[\{\text{RuCp}^*\text{Cl}\}_4]$ with a series of chiral, bidentate P,P-chelating ligands.^[35]

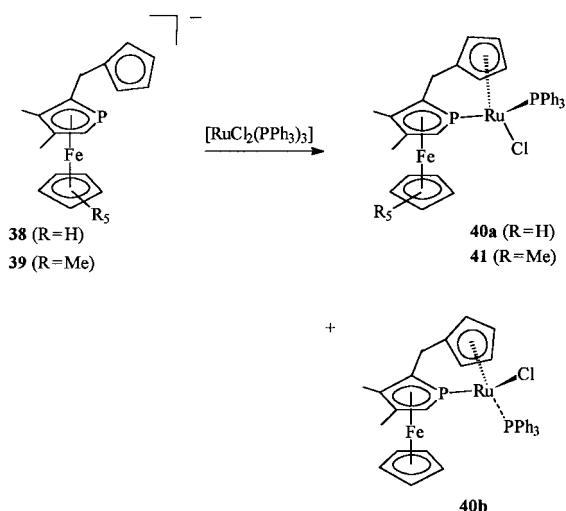
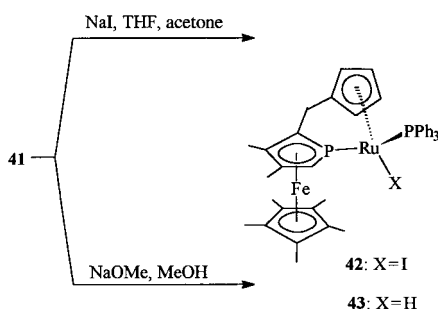
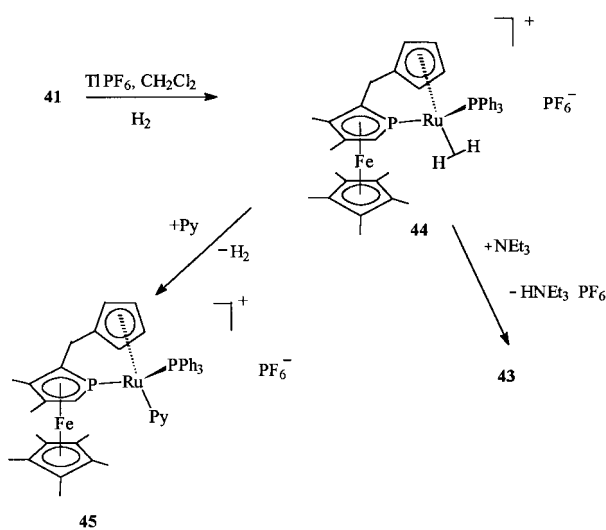


Scheme 19. Syntheses of **36** and **37**.

The planar-chiral cyclopentadienyl-functionalized phosphapherrocenes **38** and **39** are ideally suited for the diastereoselective synthesis of ruthenium half-sandwich complexes, such as **40a**, **40b**, and **41**, when **38** and **39** are treated with $[\text{RhCl}_2(\text{PPh}_3)_3]$ in toluene at 90 °C. The products were isolated in yields of 63 and 68%, respectively. Whereas complex **39** was formed as a single diastereomer, a diastereomeric ratio of 95:5 was observed with **40a** and **40b** (Scheme 20).

Compound **41** underwent a stereoselective ligand displacement to give one diastereomer of the iodo-complex **42** when treated with NaI in a mixture of acetone and THF at 20 °C. A chloride/hydride substitution to afford **43** proceeded stereoselectively with sodium methoxide in boiling methanol (Scheme 21).

Chloride abstraction from **41** by TiPF_6 in an H_2 atmosphere occurred with the formation of the cationic dihydrogen complex **44** as one single diastereoisomer. A diastereoselective displacement of the H_2 ligand to afford **45** was observed in the reaction of **44** with pyridine, whereas the employment of NEt_3 as stronger base gave rise to diastereoselective deprotonation to give **43** (Scheme 22).^[36]

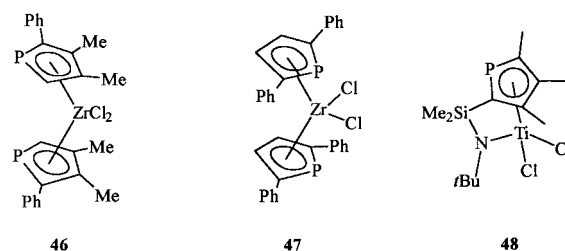

 Scheme 20. Syntheses of **40a**, **b**, and **41**.

 Scheme 21. Syntheses of **42** and **43**.

 Scheme 22. Syntheses of **44** and **45**.

4. Polymerizations and Oligomerizations

In a series of experiments under standardized conditions it was shown that phosphorus-modified zirconocene catalysts are less active in the polymerization of ethylene than their heteroatom-free analogues.^[37] Diphosphazirconocene **46**,^[38] however, served as an effective catalyst in the copolymerization of ethylene and 1-hexene in the presence of methylalu-

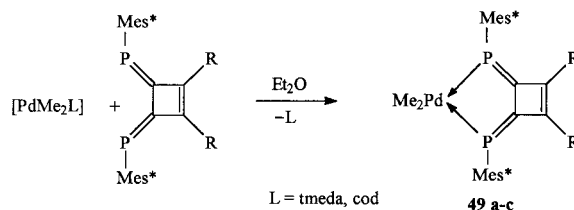
moxane (MAO). Using designations suggested by Gibson and co-workers^[39] the catalyst activity of **46** for ethylene polymerization has to be regarded as very high. Thus, 42 000 g polyethylene per mol Zr were produced per hour at 75 °C and an ethylene pressure of 7×10^5 Pa.^[38] Molecular weights M_n and M_w amount to 49 261 and 159 448 g mol⁻¹. 1-Hexene incorporation into the polymer is relatively low with butyl branch frequencies up to 3.0 per 1000 carbon atoms. Lowering the temperature to 65 °C was accompanied by a decrease in catalyst activity to only 23 647 g polyethylene per hour, whereas the average molecular weights increase to values $M_n = 93 773$ and $M_w = 254 547$ g mol⁻¹.

Bis(phospholyl)zirconium dichlorides were also successfully utilized for the production of atactic polypropylenes and oligopropylenes. Here the highest catalyst activity was with the combination of the 2,5-diphenylphospholyl system **45** with MAO at 45 °C and 600 kPa of propylene pressure (169.6 kg polypropylene g Zr⁻¹ h⁻¹; $M_n > 20 000$ g mol⁻¹).^[40, 41]



A catalyst based upon titanium complex **48** and MAO was found to polymerize ethylene at 160 °C with a similar high activity to its tetramethylcyclopentadienyl analogue. The molecular weight M_w of the polyethylene, however, was markedly lower in the case of the phosphorus containing catalyst (50×10^3 versus 126×10^3 g mol⁻¹).^[42]

Combination of [PdMe₂(tmeda)] and the diphosphinidene cyclobutanes **21b**, **c** gave the dimethylpalladium complexes **49b** and **49c** in 94 and 63 % yield, respectively. The preparation of **49a** required [PdMe₂(cod)] as a starting material (60 % yield, Scheme 23).^[43]



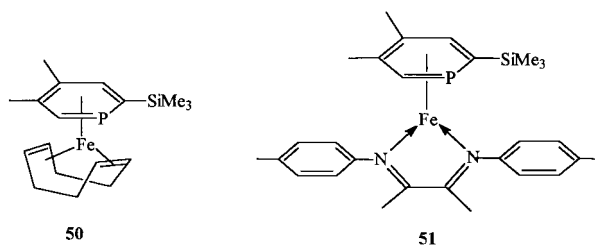
R = H (**a**); SiMe₃ (**b**); Ph (**c**)

 Scheme 23. Syntheses of **49a–c**; tmeda = *N,N,N',N'*-tetramethyl 1,2-ethanediamine.

Like their Pd-diimine analogues complexes **49a–c** are inert towards ethylene polymerization. The cationic monomethyl complexes however, which are conveniently generated from **49a–c** by treatment with H(OEt)₂B[3,5-(CF₃)₂C₆H₃]₄, are effective polymerization catalysts. The catalytic activity of the cations is sensitively determined by the nature of the

substituent R at the organophosphorus ligands. Thus, the cation derived from **49c** (R=Ph) exhibited the highest activity (128 kg polyethylene molPd⁻¹h⁻¹ yielding a polymer with a molecular weight of 18700 g mol⁻¹, which well compares with the activity of Pd/diimine catalysts.^[39, 44] Best results were obtained at 70 °C and at a pressure of 9.81 × 10⁵ Pa. Catalyst activity remained unchanged at higher pressures, although the average molecular weight decreased significantly. A remarkable feature of Yoshifuji's catalyst is its thermal stability, up to 100 °C no tendency for decomposition was noticed.^[43]

Test reactions revealed, that the η⁶-phosphabenzene iron complex **50** catalyzes the cyclotrimerization of dimethyl acetylenedicarboxylate to give C₆(CO₂Me)₆ and the co-cyclotrimerization of butyronitrile and alkynes to afford pyridine derivatives. The efficiency of **50**, however, is far below that of classical CpCo catalysts.^[45] Similar observations were made for the dimerization of 1,3-butadiene to give 1,5-cyclooctadiene under the catalysis of complex **51**.^[46]



5. Conclusions and Perspective

From the results discussed here it is clear that heterocycles with low coordination number phosphorus atoms such as phosphabenzenes and mono- and diphosphaferrocenes are valuable as efficient modifying ligands in homogeneous catalysis. A number of papers underline their pronounced π-acceptor capability, which makes phosphabenzenes and phosphaferrrocenes ideal as ligands for the soft metal centers usually present in catalytically active complexes. Planar-chiral structures at the ferrocene framework are prerequisites for the well-tailored design used in enantioselective, asymmetric syntheses.

The remarkable results, achieved by less than 10 research groups and in less than 10 years of research activity in this area of academic and commercial interest, are promising for the future development and improvement of highly efficient and stereoselective catalysts. Without exaggeration the chemistry of phosphorus–carbon heterocycles may well be regarded as a gold mine for new sp²-ligands which are able to confer unusual properties upon metal centers and the substrates there coordinated.

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News about Oxygen

Detlef Schröder*

Within the last decade, rapid improvements in the development of quantum chemical methods as well as computers have enabled theoreticians to pose several provocative questions to experimentalists engaged in the chemistry of oxygen.

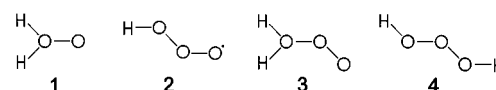
"Is there a transition state for the unimolecular dissociation of cyclooctaoxygen (O_8)?"^[1]

"Can oxywater be made?"^[2]

"How long can you make an oxygen chain?"^[3]

Meanwhile, some of these, as well as several related aspects of neutral H_mO_n compounds ($m = 0-2$, $n = 2-4$), have been addressed experimentally using neutralization–reionization (NR) mass spectrometry.^[4, 5] The NR method starts with the generation of the corresponding ionic species, which are then accelerated to kinetic energies of several keV, mass selected, and neutralized by vertical electron transfer (ET) in a high-energy collision. After removal of all ionic species, the remaining, still fast-moving neutrals are reionized in another keV collision, mass-analyzed, and detected (Figure 1). The

After the NR method had been successfully applied for the detection of the elusive oxywater **1**^[7] the group of Cacace at the University of Rome systematically investigated oxygen chemistry, and several H_mO_n species have been shown to exist as long-lived neutrals in the gas phase.^[8–10] Parallel work of



Speranza and co-workers from the very same faculty has provided valuable energetic information about species such as **2–4**.^[11, 12] For example, the $HO_3^{\cdot}$ radical **2**, has repeatedly been postulated as an important intermediate in atmospheric processes, although it has never been detected experimentally. In particular, it was not clear whether the combination of atomic hydrogen with ozone might lead to a long-lived $HO_3^{\cdot}$ radical or if immediate dissociation into O_2 and $HO^{\cdot}$ takes place. In 1999, NR experiments conducted by Cacace et al. with mass-selected HO_3^+ ions generated from protonated ozone, proved the existence of the neutral $HO_3^{\cdot}$ radical in the μs range,^[9] thereby corroborating the need for the inclusion of this species in the modeling of the atmospheric chemistry of ozone.

The particular stimulus for this Highlight is the recent detection of a long-lived O_4 species by the Cacace group.^[13] The interest in oxygen modifications other than O_2 and O_3 has two facets. On the one hand, formation of transient O_4 has been postulated to affect the ozone concentrations in the lower stratosphere by reactions with atomic oxygen [Eq. (1)].^[14] On the other hand, higher oligomers of oxygen



O_n ($n = 4, 6, 8, 12$) have been investigated theoretically in the search for high-energy dense materials (HEDM) to be used as possible rocket propellants or explosives. For example, cyclic O_8 has been predicted by theory to exist as a high-energy modification of oxygen in analogy to cyclooctasulfur S_8 , and O_8 can indeed be considered as an HEDM because dissociation into four O_2 molecules is predicted to be exothermic by about 95 kcal mol^{-1} .^[15] As far as the O_4 molecule is concerned, the various theoretical predictions made so far are somewhat divergent. The spread of the theoretical results is not at all unexpected, however, because a molecule such as O_4 imposes

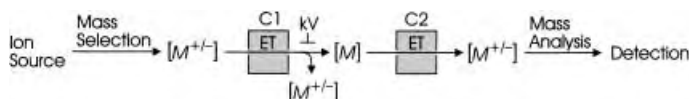


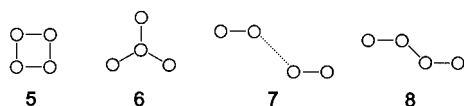
Figure 1. Schematic representation of an NR experiment.^[4, 5] A mass-selected beam of cationic or anionic projectiles $M^{\pm}$ generated in the ion source is neutralized in a first collisional ET in the collision cell C1. Subsequently, all the charged species are deflected by a kV voltage leaving a beam of fast-moving neutrals which enters a second collision cell C2 where reionization by a second ET takes place. The ionic species formed are then mass analyzed and detected by conventional mass spectrometric means.

NR method typically samples neutrals having lifetimes within or exceeding the μs regime. While this interval appears to be rather short, it is in fact almost an eternity for small systems such as the H_mO_n species considered here because the entire rovibrational manifold, which includes formally spin-forbidden reactions, can exhaustively be explored in this period.^[6]

[*] Dr. D. Schröder
Institut für Chemie
Technische Universität Berlin
Strasse des 17. Juni 135, 10623 Berlin (Germany)
Fax: (+49) 30-314-21102
E-mail: df@www.chem.tu-berlin.de

extreme demands to the description of electron correlation, symmetry breaking as well as significant multi-reference character of the wavefunctions is to be expected, and finally, spin-orbit coupling must be included in a proper assessment of the kinetic stability of O_4 . The most recent study does indeed suggest that the singlet state of cyclotetraoxygen is kinetically stabilized by a barrier of about 6 kcal mol^{-1} with respect to the very exothermic dissociation into two (triplet) O_2 molecules.^[16]

The NR experiments of Cacace et al.^[13] have now established unambiguously that neutral O_4 can exist as a transient in the μs regime. To this end, chemical ionization (CI) of dioxygen was used to generate O_4^{+*} radical cations^[17] which were then mass-selected and subjected to a NR sequence. Distinct recovery signals, clearly arising from neutral O_4 , were observed for all isotopic combinations examined in these NR experiments. The flip side of the coin is, however, that the various experimental findings were incompatible with the theoretical predictions for the covalent O_4 species considered so far. At first, isotopic labeling disfavors the cyclic structure **5** of the neutral O_4 transient because the NR spectrum of



$^{16}O_2^{18}O_2^{+*}$ (formed by CI of a $^{16}O_2/^{18}O_2$ mixture) gives rise to $^{16}O_2^{+*}$ and $^{18}O_2^{+*}$ fragments in almost equal abundancies, but very little $^{16}O^{18}O^{+*}$. However, a 1:2:1 ratio of $^{16}O_2^{+*}$, $^{16}O^{18}O^{+*}$, and $^{18}O_2^{+*}$ is expected for a cyclic structure, and similar arguments apply to a possible pinwheel structure **6** ("ozone oxide"). In turn, generation of a mere van der Waals complex **7** also appears improbable, because the NR experiments proceed as a sequence of vertical ET steps in high-energy collisions which is rather unlikely to be survived by the $[O_2 \cdot O_2]$ van der Waals complex, which has a binding energy of less than 1 kcal mol^{-1} .^[18] While the experimental results might be explained by invoking an acyclic, covalently bound O_4 isomer, none of the previous theoretical studies gives any indication that such a species is stable. Hence, we arrive at a situation where the result of the NR study itself is unambiguous in that transient neutral O_4 exists, while the nature of the species formed remains unknown.^[19] Cacace et al.^[13] suggest the formation of a bound molecule, formally described as $[O_2^* \cdot O_2]$ (**8**) which arises from excited states of dioxygen which themselves have also been suggested to participate in atmospheric processes such as the ozone cycle and terrestrial and venusian nightglows.^[20]

Even more than 200 years after the "discovery" of oxygen,^[21] speculation about new modifications of oxygen is not restricted to the peculiar conditions of the idealized gas phase. In an entirely different context, a group of Italian physicists has recently provided independent evidence for the existence of O_4 in the ϵ -phase of solid oxygen formed at high pressures.^[22] Further, a group at the Lawrence Livermore

National Laboratory (USA) presented evidence for the existence of metallic modifications of oxygen at very large pressures of up to 2 Mbar.^[23, 24]

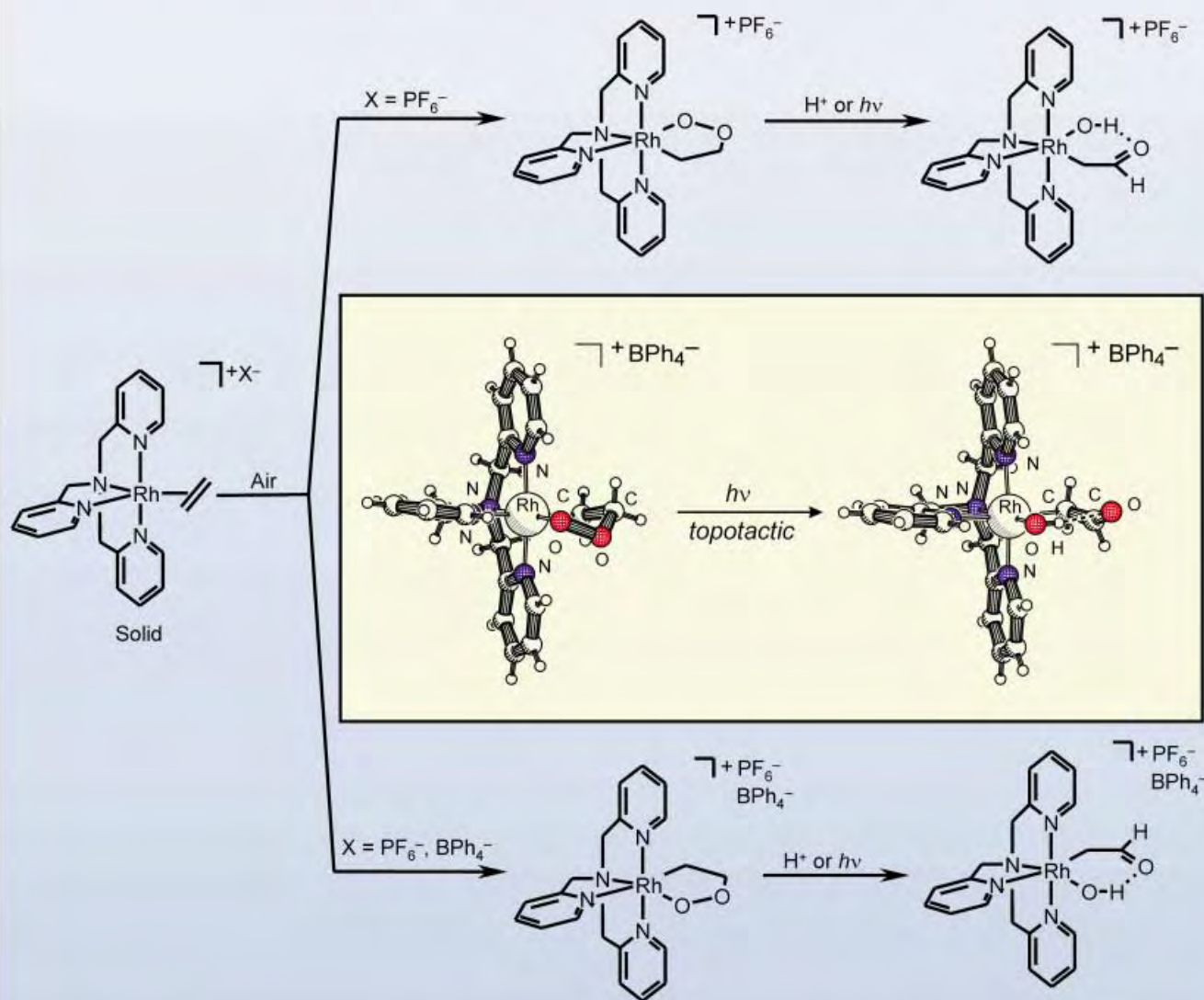
Notwithstanding these new experimental observations, an extension to a preparative scale, or an isolation of O_4 , cannot be foreseen. Hence, theoretical assistance is needed again in the search for new O_4 molecules which exhibit lifetimes in the μs regime (or more) and are likely to survive a sequence of keV collisions occurring in NR experiments. In other words, the ball thrown out by theoreticians bounces back to them once more. Let us await whether or not the next round can provide more definitive information about the existence and identity of new allotropes of oxygen.

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Dioxygen activation in progress

Dioxygen reacts with ethene complexes to 3-rhoda-1,2-dioxolanes and subsequently breaks its O–O bond.



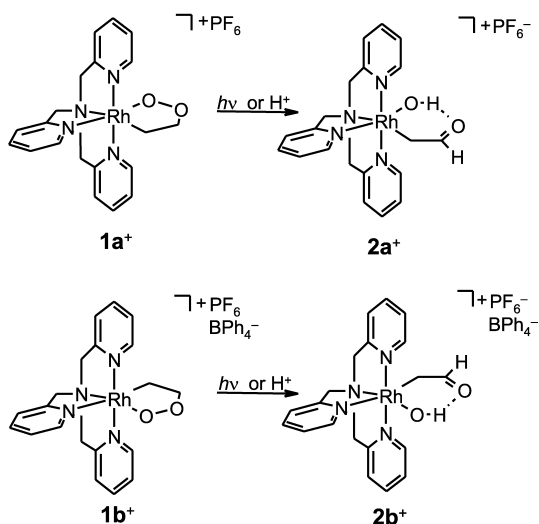
Exposure of a single crystal of a rhodadioxolane to light results in topotactic transformation to a rhodium formylmethyl hydroxy complex.

More about this rearrangement, which contradicts earlier proposed conversions of 3-metalla-1,2-dioxolanes, can be found on the following pages.

Rearrangement of 3-Rhoda-1,2-dioxolanes to Rhodium Formylmethyl Hydroxy Complexes**

Monique Krom, Ruud G. E. Coumans, Jan M. M. Smits, and Anton W. Gal*

3-Metalla-1,2-dioxolanes have been proposed as intermediates in catalytic oxidation of olefins by metals of Groups 6 and 8–10.^[1] We previously reported the formation of the stable 3-rhoda-1,2-dioxolanes **1a**⁺ and **1b**⁺ (Scheme 1) by reaction of solid rhodium ethene complexes of the N₄ ligand tris-(2-pyridylmethyl)amine (tpa) with air.^[2] We now report their rearrangement to rhodium formylmethyl hydroxy complexes upon exposure to light or protons.



Scheme 1. Rearrangement of 3-rhoda-1,2-dioxolanes to rhodium formylmethyl hydroxy complexes.

Exposure of microcrystalline **1b**-BPh₄ to glass-filtered daylight under N₂ resulted in selective conversion to the corresponding rhodium formylmethyl hydroxy complex **2b**-BPh₄ over several weeks (Scheme 1). Similarly, exposure of a solution of **1b**-BPh₄ in CD₃CN to the glass-filtered light from a high-pressure mercury lamp at –30 °C resulted in conversion to **2b**-BPh₄. The ¹H NMR spectrum of the resulting solution indicated that an optimum yield of 90 % **2b**-BPh₄ was obtained after 90 min of illumination.

The ESI-MS spectrum of **2b**⁺ is the same as that of **1b**⁺,^[2] with the exception of a peak at *m/z* = 435, which corresponds to loss of water from the parent cation. Such loss of water in

the gas phase was observed earlier for the transient formylmethyl hydroxy complex [(MeCN)(κ³-Bzbp)Rh(κ¹-CH₂CHO)(OH)]BPh₄, the only formylmethyl hydroxy complex reported thus far.^[3,4]

The ¹H NMR and ¹³C NMR spectra of **2b**-BPh₄ reveal the presence of a formylmethyl fragment [¹H NMR: δ = 2.69 (dd, ³*J*(H,H) = 5.1, ²*J*(H,Rh) = 2.9 Hz, RhCH₂CHO) and 9.26 (t, ³*J*(H,H) = 5.1 Hz, RhCH₂CHO); ¹³C NMR: δ = 26.9 (d, ¹*J*(C,Rh) = 21.0 Hz, RhCH₂CHO) and 209.0 (RhCH₂CHO)]. The ¹H NMR signals for the formylmethyl group of **2b**⁺ are comparable to those of [(MeCN)(κ³-Bzbp)Rh(κ¹-CH₂CHO)(OH)]BPh₄ [δ = 3.37 (dd, ³*J*(H,H) = 5.3, ²*J*(H,Rh) = 2.9 Hz, RhCH₂CHO) and 10.3 (t, ³*J*(H,H) = 5.3 Hz, RhCH₂CHO)].^[4] Formylmethyl hydroxy complex **2b**⁺ shows a strong IR absorption for a carbonyl group at 1655 cm^{–1}.

After repeated attempts to obtain X-ray quality crystals of **2b**-BPh₄ had failed, an attempt was made to photochemically convert a single crystal of **1b**-BPh₄ to a single crystal of **2b**-BPh₄. The crystal that was used for X-ray structure determination of **1b**-BPh₄^[2] was exposed to glass-filtered daylight for one week, and its crystal structure was re-determined.^[5] It was found that **1b**⁺ had been fully converted to **2b**⁺ in a topotactic transformation that left the crystal packing virtually unchanged.^[6] The crystal structure of **2b**⁺ shows that the hydroxy group forms a hydrogen bond with the formyl fragment in a puckered six-membered ring (Figure 1). The bridging hydrogen atom H1 was localized at an O1–H1 distance of 0.80(5) Å (Rh–O1–H1 99(4)°) and an H1–O2 distance of 1.92(5) Å (O1–H1–O2 168(5)°), well within the range of hydrogen bonding. The puckering of the six-membered ring results from rotation of the formyl group around the C1–C2 bond (torsion angle Rh–C1–C2–O2 = 72(3)°).

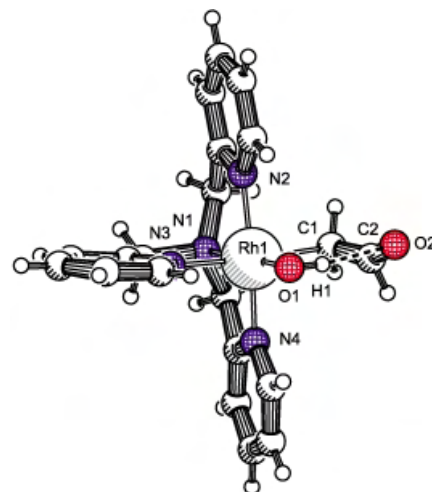


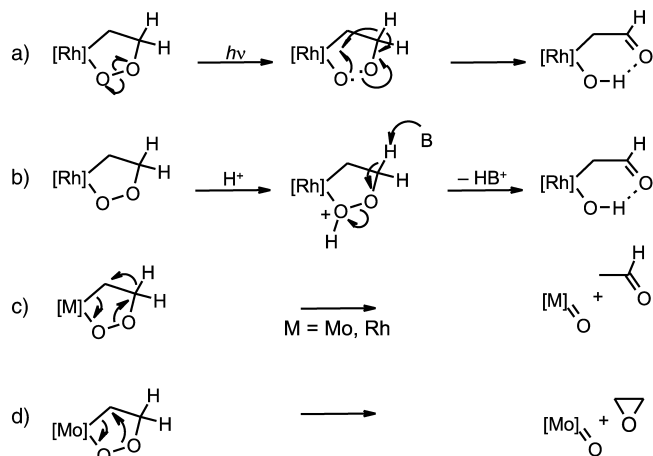
Figure 1. X-Ray structure of rhodium formylmethyl hydroxy complex **2b**⁺. Selected bond lengths [Å]: Rh1–N1 2.040(3), Rh1–N2 2.018(4), Rh1–N3 2.102(3), Rh1–N4 2.033(4), Rh1–C1 2.085(4), Rh1–O1 2.014(3), O2–C2 1.103(11), C1–C2 1.245(12), H1–O2 1.92(5), O1–H1 0.80(5).

We propose that the photochemical rearrangement of **1b**⁺ to **2b**⁺ involves photolysis of the O–O bond followed by abstraction of a β-hydrogen atom from CH₂CH₂O• by O• (Scheme 2a). This β-hydrogen abstraction is probably facili-

[*] Prof. Dr. A. W. Gal, M. Krom, R. G. E. Coumans, J. M. M. Smits
Department of Inorganic Chemistry, University of Nijmegen
Toernooiveld 1, 6525 ED Nijmegen (The Netherlands)
Fax: (+31) 24-355-3450
E-mail: gal@sci.kun.nl

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

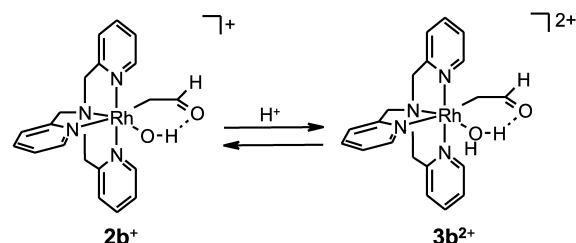


Scheme 2. Mechanisms for rearrangement of a 3-metalla-1,2-dioxolane: a) photochemically to a formylmethyl hydroxy complex, b) proton-assisted to a formylmethyl hydroxy complex, c) directly to an oxo complex and acetaldehyde,^[1a,d] and d) directly to an oxo complex and ethylene oxide.^[1d]

tated by the envelope structure of the 3-rhoda-1,2-dioxolane moiety,^[2] which positions one β -hydrogen atom close to O1.

Analogous to microcrystalline 3-rhoda-1,2-dioxolane **1b**-BPh₄, the microcrystalline mixture of the isomeric 3-rhoda-1,2-dioxolanes **1a**-PF₆ and **1b**-PF₆ (**1a**-PF₆/**1b**-PF₆) rearranged photochemically to a mixture of the isomeric formylmethyl hydroxy complexes **2a**-PF₆ and **2b**-PF₆ (**2a**-PF₆/**2b**-PF₆; Scheme 1). However, **1b**-BPh₄ and **1a**-PF₆/**1b**-PF₆ reacted differently upon exposure to an N₂ atmosphere saturated with H₂O; whereas **1b**-BPh₄ proved stable, **1a**-PF₆/**1b**-PF₆ rearranged to **2a**-PF₆/**2b**-PF₆. Since **1b**-BPh₄ and **1a**-PF₆/**1b**-PF₆ both proved stable under dry N₂, this reactivity must have been triggered by the presence of H₂O. It may result from protonation of the rhodadioxolane by traces of HF, formed by hydrolysis of PF₆⁻.

As the ³¹P NMR spectrum (120 MHz) of the mixture of formylmethyl hydroxy complexes did not reveal signals of the hydrolysis product PF₂O₂⁻, we decided to investigate proton-assisted ring opening in solution. Therefore, 0.1 equiv of the noncoordinating acid [H(OEt₂)₂]B[C₆H₃(CF₃)₂]₄ (HBAr₄^F) was added to a solution of **1b**-BPh₄ in CD₃CN. ¹H NMR spectroscopy showed that **1b**⁺ is converted within 1 h to formylmethyl hydroxy complex **2b**⁺ in approximately 70% yield. Likewise, addition of 1.1 equiv of HBAr₄^F to a solution of **1b**-BPh₄ gave formylmethyl aqua complex **3b**²⁺ (that is, protonated **2b**⁺) in approximately 85% yield within 10 min (Scheme 3).^[7] In the latter case any **2b**⁺ formed is apparently directly protonated. This protonation results in a downfield



Scheme 3. Protonation of rhodium formylmethyl hydroxy complex **2b**⁺ to rhodium formylmethyl aqua complex **3b**²⁺.

shift of the RhCH₂CHO and RhCH₂CHO ¹H NMR signals from δ = 2.69 to δ = 3.05 and from δ = 9.26 to δ = 9.51, respectively. The base peak in the ESI-MS spectrum of the obtained solution has the correct isotope distribution pattern and m/z value (227) for **3b**²⁺. As evidenced by its formylmethyl ¹H NMR signals, a trace of **3b**²⁺ also forms in the conversion of solid **1a**-PF₆/**1b**-PF₆ to **2a**-PF₆/**2b**-PF₆ under N₂ saturated with H₂O. This seems to confirm our hypothesis of HF-catalyzed ring opening.

A possible mechanism for the acid catalyzed ring opening is shown in Scheme 2b. Protonation of **1b**⁺ at O_a induces heterolytic splitting of the O–O bond, followed by formation of a carbonyl double bond and deprotonation at C _{β} by an external base.

The isomeric 3-rhodadioxolanes **1a**⁺ and **1b**⁺ clearly differ in their photoreactivity: upon exposure of a CD₃CN solution of **1a**⁺ and **1b**⁺ to glass-filtered daylight at room temperature, the relative intensities of the 2-peroxyethyl ¹H NMR signals show that the initial reaction rate of **1a**⁺ is three times higher than that of **1b**⁺ (Figure 2).

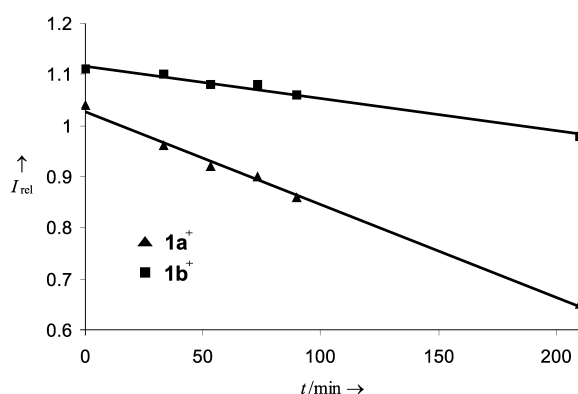


Figure 2. Relative intensities of the 2-peroxyethyl ¹H NMR signals of **1a**⁺ and **1b**⁺ on exposure to glass-filtered daylight.

The observed rearrangement of 3-rhoda-1,2-dioxolanes to formylmethyl hydroxy complexes is in marked contrast to the direct rearrangement of a 3-metalla-1,2-dioxolane to a metal oxo complex and acetaldehyde (as proposed for 3-rhoda-1,2-dioxolanes and calculated for 3-molybdena-1,2-dioxolanes; Scheme 2c)^[1a, 8] or to a metal oxo complex and ethylene oxide (as proposed for 3-molybdena-1,2-dioxolanes).^[1d] The reactivity of the rhodium formylmethyl hydroxy and formylmethyl aqua complexes is currently being investigated.

Experimental Section

The NMR spectra were recorded on Bruker DPX200 and AM500 spectrometers. Shifts are reported relative to CD₃CN: δ (¹H) = 1.94, δ (¹³C) = 118.1. ESI-MS spectra were recorded on Finnigan TSQ 7000 and MAT 900S mass spectrometers. Infrared spectra were recorded on a Perkin-Elmer 1720X spectrometer.

Compounds [(CH₂CH₂)₂RhCl]₂,^[9] tpa,^[10] [(tpa)Rh(κ^2 C¹O²-OOCH₂CH₂)]-BPh₄/PF₆,^[2] and [H(OEt₂)₂]B[C₆H₃(CF₃)₂]₄ (HBAr₄^F)^[11] were prepared according to literature procedures.

2a-PF₆/**2b**-PF₆: Solid **1a**-PF₆/**1b**-PF₆ was exposed to an N₂ atmosphere saturated with H₂O for 3 d at room temperature. A mixture of **2a**-PF₆ and **2b**-PF₆ was obtained in an approximate ratio of 1:1. **2a**-PF₆: ¹H NMR (500 MHz, CD₃CN, 243 K): δ = 9.98 (t, 1H, ³J(H,H) = 4.9 Hz,

RhCH₂CHO), 8.68 (d, 2H, ³J(H,H)=5.5 Hz, Py_b-H6), 8.53 (d, 1H, ³J(H,H)=5.5 Hz, Py_a-H6), 7.84 (m, 2H, Py_b-H4), 7.66 (dt, 1H, ³J(H,H)=7.7, ⁴J(H,H)=1.5 Hz, Py_a-H4), 7.48 (d, 2H, ³J(H,H)=8.2 Hz, Py_b-H3), 7.36 (t, 2H, ³J(H,H)=6.6 Hz, Py_b-H5), 7.28 (t, 1H, ³J(H,H)=6.6 Hz, Py_a-H5), 7.17 (d, 1H, ³J(H,H)=8.8 Hz, Py_a-H3), 5.39 (d(AB), 2H, ²J(H,H)=15.0 Hz, NCH₂Py_b), 4.88 (s, 2H, NCH₂Py_a), 4.76 (d(AB), 2H, ²J(H,H)=15.0 Hz, NCH₂Py_b), 3.47 (dd, 2H, ³J(H,H)=4.8, ²J(H,Rh)=2.9 Hz, RhCH₂CHO); ¹³C{¹H} NMR (125 MHz, CD₃CN, 243 K): δ = 210.8 (d, ²J(C,Rh)=9.6 Hz, RhCH₂CHO), 165.0 (Py_b-C2), 163.5 (Py_a-C2), 151.5 (Py_b-C6), 150.2 (Py_a-C6), 139.6 (Py_b-C4), 138.8 (Py_a-C4), 125.4 (Py_b-C5/C3), 125.1 (Py_a-C5/C3), 124.4 (Py_b-C5/C3), 122.1 (Py_a-C5/C3), 66.4 (NCH₂Py_b), 66.2 (NCH₂Py_a), 34.5 (d, ¹J(C,Rh)=25.0 Hz, RhCH₂CHO); ESI-MS (CH₃CN): 453 [M – PF₆]⁺.

2b-BPh₄: Method A: A stirred solution of **1b-BPh₄** in CD₃CN under nitrogen was exposed to the glass-filtered light from a high-pressure mercury vapor lamp^[12] for 90 min at –30 °C. **2b-BPh₄** was obtained in >90 % yield, as determined by ¹H NMR spectroscopy. Method B: HBAR₄^F (5.5 mg, 5.4 μmol) was added to a solution of **1b-BPh₄** (41.8 mg, 54 μmol) in CD₃CN (1 mL) under N₂. **2b-BPh₄** was obtained in approximately 70 % yield after about 1 h, as determined by ¹H NMR spectroscopy. ¹H NMR (200 MHz, CD₃CN, 300 K): δ = 9.26 (t, 1H, ³J(H,H)=5.0 Hz, RhCH₂CHO), 9.21 (brd, 1H, ³J(H,H)=6.0 Hz, Py_a-H6), 8.62 (brd, 2H, ³J(H,H)=5.6 Hz, Py_b-H6), 7.84 (dt, 2H, ³J(H,H)=7.8, ⁴J(H,H)=1.6 Hz, Py_b-H4), 7.73 (dt, 1H, ³J(H,H)=7.8, ⁴J(H,H)=1.6 Hz, Py_a-H4), 7.32 (m, 6H, Py_b-H3, Py_b-H5), 7.27 (m, 8H, BAR-H2), 6.99 (t, 8H, ³J(H,H)=7.4 Hz, BAR-H3), 6.83 (t, 4H, ³J(H,H)=7.2 Hz, BAR-H4), 5.01 (d(AB), 2H, ²J(H,H)=15.9 Hz, NCH₂Py_b), 4.71 (d(AB), 2H, ²J(H,H)=14.9 Hz, NCH₂Py_b), 4.67 (s, 2H, NCH₂Py_a), 2.69 (dd, 2H, ³J(H,H)=5.1, ²J(H,Rh)=2.9 Hz, RhCH₂CHO); ¹³C{¹H} NMR (125 MHz, CD₃CN, 243 K): δ = 209.0 (RhCH₂CHO), 163.9 (q, ¹J(C,B)=49.2 Hz, BAR-C1), 162.4 (Py_b-C2), 159.0 (Py_a-C2), 149.9 (Py_b-C6), 147.2 (Py_a-C6), 139.3 (Py_b-C4), 139.2 (Py_a-C4), 135.7 (BAR-C2), 126.1 (q, ³J(C,B)=2.7 Hz, BAR-C3), 125.4 (Py_b-C5/C3), 124.9 (Py_a-C5/C3), 124.4 (Py_b-C5/C3), 122.1 (BAR-C4), 121.2 (Py_a-C5/C3), 70.7 (NCH₂Py_a), 68.3 (NCH₂Py_b), 26.9 (d, ¹J(C,Rh)=21.0 Hz, RhCH₂CHO); ESI-MS (CD₃CN): 453 [M – BPh₄]⁺, 435 [M – H₂O – BPh₄]⁺, 425 [M – C₂H₄ – BPh₄]⁺, 409 [M – C₂H₄O – BPh₄]⁺, 393 [M – C₂H₄O₂ – BPh₄]⁺, 391 [M – C₂H₄O₂ – H₂ – BPh₄]⁺; IR (KBr): 1655 cm^{–1}.

3b-BPh₄/BAR₄^F: HBAR₄^F (57 mg, 0.11 mmol) was added to a solution of **1b-BPh₄** (40 mg, 0.1 mmol) in CD₃CN (1.0 mL) under N₂. **3b-BPh₄/BAR₄^F** was obtained in approximately 85 % yield as determined by ¹H NMR spectroscopy. ¹H NMR (200 MHz, CD₃CN, 300 K): δ = 9.51 (t, 1H, ³J(H,H)=4.8 Hz, RhCH₂CHO), 8.96 (d, 1H, ³J(H,H)=5.5 Hz, Py_a-H6), 8.52 (d, 2H, ³J(H,H)=5.7 Hz, Py_b-H6), 7.95 (dt, ³J(H,H)=7.8, ⁴J(H,H)=1.6 Hz, Py_b-H4), 7.81 (dt, ³J(H,H)=7.8 Hz, ⁴J(H,H)=1.6 Hz, Py_a-H4), 7.73 (m, 8H, BAR₄^F-H2), 7.68 (s, 4H, BAR₄^F-H4), 7.6–7.4 (m, 5H, Py_b-H3, Py_b-H5, Py_a-H3/5), 7.33 (m, 8H, BAR-H2), 7.21 (m, 1H, Py_a-H3/5), 7.01 (t, 8H, ³J(H,H)=7.4 Hz, BAR-H3), 6.85 (t, 4H, ³J(H,H)=6.9 Hz, BAR-H4), 5.15 (d(AB), 2H, ²J(H,H)=16.4 Hz, NCH₂Py_b), 4.82 (s, 2H, NCH₂Py_a), 4.69 (d(AB), 2H, ²J(H,H)=16.6 Hz, NCH₂Py_b), 3.05 (dd, 2H, ³J(H,H)=4.9, ²J(H,Rh)=2.7 Hz, RhCH₂CHO); ¹³C{¹H} NMR (125 MHz, CD₃CN, 243 K): δ = 206.7 (d, ²J(C,Rh)=1.9 Hz, RhCH₂CHO), 164.0 (q, ¹J(C,B)=49.2 Hz, BAR-C1), 161.9 (q, ¹J(C,B)=49.8 Hz, BAR^F-C1), 161.6 (Py_b-C2), 158.0 (Py_a-C2), 151.5 (Py_b-C6), 148.7 (Py_a-C6), 140.9 (Py_b-C4), 140.4 (Py_a-C4), 135.8 (BAR-C2), 134.9 (BAR^F-C2), 129.0 (qq, ²J(C,F)=31.4 Hz, ³J(C,B)=2.9 Hz, BAR^F-C3), 126.4 (Py_b-C5/C3), 126.2 (q, ³J(C,B)=2.6 Hz, BAR-C3), 125.8 (Py_a-C5/C3), 125.4 (Py_b-C5/C3), 124.6 (q, ¹J(C,F)=271.9 Hz, BAR^F-CF₃), 122.3 (BAR-C4), 122.1 (Py_a-C5/C3), 73.5 (NCH₂Py_a), 69.6 (NCH₂Py_b), 27.8 (d, ¹J(C,Rh)=20.4 Hz, RhCH₂CHO). The signal for BAR^F-C4 is obscured by one of the solvent signals. ESI-MS (CH₃CN): 227 [M – BPh₄ – BAR₄^F]²⁺, 218 [M – H₂O – BPh₄ – BAR₄^F]²⁺.

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- [5] A transparent yellow crystal of **2b-BPh₄** was obtained by exposure of a crystal of **1b-BPh₄** (obtained by slow diffusion of diethyl ether into a 1,2-dichloroethane/acetonitrile solution^[2]) to glass-filtered daylight for one week. The X-ray diffraction data were collected at 150(2) K on an Enraf-Nonius CAD4 diffractometer with rotating anode and CCD area detector with graphite-monochromatized MoK_α radiation (λ = 0.71073 Å). The structure was solved by the PATTY^[13] option of the DIRDIF^[14] program package. Crystal data: C₄₈H_{50.50}BCIN_{4.50}O_{2.50}Rh, *M_r* = 879.60, monoclinic, space group C2/c, *a* = 36.0362(2), *b* = 10.77600(10), *c* = 24.2975(2) Å, β = 116.3883(4)°, *V* = 8452.21(11) Å³, *Z* = 8, ρ_{calcd} = 1.382 Mg m^{–3}. All non-hydrogen atoms were refined with anisotropic temperature factors. The hydrogen atoms, except H1, were placed at calculated positions and refined isotropically in riding mode. H1 was clearly observed in a difference Fourier map, and its position was subsequently determined automatically. Its positional and thermal parameters were refined freely, and this refinement proved to be stable. The position of H1 is well outside the regions influenced by the SQUEEZE procedure described below. From the anisotropic thermal displacement parameters for C2 and O2 it is clear that these atoms show a large positional disorder. Although it is possible to use several partially occupied positions for these atoms, no physically reasonable models result from these parameters, and none is any better than the model presented here. Splitting these atoms serves no other purpose than to lower the *R* value. The calculated hydrogen positions on C2 are therefore merely indications of possible positions. Calculations (PLATON, Spek 1995)^[15] showed two distinct voids, one of 239 Å³ containing 58 electrons around a twofold axis (position 4e, 0, *y*, 1/4; *y* = –0.041), and one of 152 Å³ containing 39 electrons around an inversion center (position 4b: 1/2, 0, 0). Based on the synthetic route and evidence from NMR spectroscopy it is assumed that these electron densities possibly represent one molecule of diethyl ether (C₄H₁₀O, 42 electrons) plus one molecule acetonitrile (CH₃CN, 22 electrons) in the first void (64 electrons, 29.9 Å³/non-hydrogen atom), and one molecule of dichloroethane (C₂H₄Cl₂, 50 electrons) in the second (38.0 Å³/non-hydrogen atom). These assumptions are in accordance with the earlier crystal structure determination of the original crystal of **1b-BPh₄** before its exposure to glass-filtered daylight^[2] and account for the calculated physical molecular properties as reported in this paper. It was not possible to assign any physically meaningful parameters to the electron densities found in the difference Fourier map. Therefore the SQUEEZE procedure was applied to account for these electron densities. CCDC-170096 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
- [6] Space group before and after transformation: C2/c. Cell dimensions before transformation: *a* = 35.8688(5) Å, *b* = 10.7328(2) Å, *c* = 24.2609(4) Å, β = 116.666(1)°, *V* = 8346.4(3) Å³. Cell dimensions after transformation: *a* = 36.0362(2) Å, *b* = 10.7760(1) Å, *c* = 24.2975(2) Å, β = 116.3883(4)°, *V* = 8452.2(2) Å³.
- [7] The longer reaction time and lower yield upon addition of 0.1 equiv HBAR₄^F can be explained by the lower acidity of the solution and slow decomposition of **2b**⁺. The absence of the aqua complex **3b**²⁺ in the resulting reaction mixture can be explained by its slow conversion to **2b**⁺ through proton abstraction by BPh₄[–]. Acid decomposition of BPh₄[–] to BPh₃ and benzene is described in H. Nishida, N. Takada, M. Yoshimura, T. Sonoda, H. Kobayashi, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600, and references therein.
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Paramagnetic Keplerate “Necklaces” Synthesized by a Novel Room-Temperature Solid-State Reaction: Controlled Linking of Metal-Oxide-Based Nanoparticles**

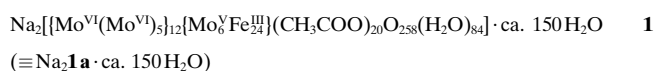
Achim Müller,* Samar K. Das, Marina O. Talismanova,
Hartmut Bögge, Paul Kögerler, Marc Schmidtman,
Sergei S. Talismanov, Marshall Luban, and
Erich Krickemeyer

*Dedicated to Professor C. N. R. Rao on the occasion of the
Silver Jubilee of his Solid State and Structural Chemistry Unit*

The search for extended structures based on linked nano-sized stable building blocks especially with well-defined electronic and magnetic properties is an extremely worthy task because such multidimensional networks could result in new types of functionalized materials.^[1] In this context we are involved in the synthesis of ever larger well-defined metal-oxide-based nanoparticles with unique host properties and their linking through M–O–M- or M–O–M'-type bonds to obtain a wide range of architectures.^[2] For instance, spherical metal-oxide-based Keplerate-type clusters with icosahedral symmetry, which exhibit an internal cavity (diameter) large

enough to even encapsulate Keggin-type clusters—thus leading to remarkable composites—can be generated in a facile synthesis.^[3] The Keplerate-type clusters also display interesting topologies.^[4] So far there has been no report on the linking of such large spherical objects to form a chain structure (for very interesting fullerene-type systems see ref. [5]). Here we report the synthesis and structure of an unusual mixed-valence compound^[6] containing discrete {Mo^{VI}(Mo^{VI})₅}₁₂{Mo^VFe^{III}}_{24}-type Keplerate clusters and their one-dimensional linking by a novel type of solid-state reaction at room temperature to form chains. We also present a theoretical model based on a modification of a {Mo^{VI}(Mo^{VI})₅}₁₂{Fe^{III}}_{30} prototype^[7] that helps to explain the measured magnetic properties of the chain compound.

If a strongly acidified aqueous solution of sodium molybdate is treated with ferrous chloride in the presence of air and a rather high concentration of acetic acid, black crystals of **1** containing {Mo^{VI}(Mo^{VI})₅}₁₂{Mo^VFe^{III}}_{24}-type anionic clusters precipitate, which upon drying at room temperature get linked to chains, yielding (the black) compound **2** (see also Experimental Section).



During the formation process, the Fe^{II} ions partly reduce the Mo^{VI} centers though most of the Fe^{II} cations are oxidized by air to Fe^{III}. In any case the presence of Fe^{II} is necessary, as beginning the synthesis with Fe^{III} as starting material in the presence of a reducing agent leads immediately to a non-crystalline precipitate.

Whereas compound **2** was characterized to a full extent by elemental analysis, thermogravimetry (to determine the crystal water content), bond valence sum (BVS) calculations,^[8] spectroscopic methods (IR, resonance Raman, VIS-NIR, ⁵⁷Fe Mössbauer) as well as magnetic measurements and single-crystal structure analysis,^[9] compound **1**, which contains discrete spherical clusters, could only be identified by single-crystal X-ray structure analysis of the non-dried crystals. These crystals were cooled immediately to liquid nitrogen temperature to block any further release of water and subsequent condensation reactions which would lead to the formation of **2**.^[9]

Both the spherical cluster anion **1a** and the spherical building blocks of the anion chain **2a** comprise 12 pentagonal fragments of the type {Mo^{VI}(Mo^VO)₁₂} (containing a central pentagonal MoO₇ bipyramid edge-sharing with five {MoO₆} octahedra) which are connected by 24 {Fe^{III}(H₂O)₂}³⁺^[10] and six {Mo^VO(H₂O)}³⁺ linkers (the six Mo(4d) electrons are also partially delocalized over the Mo positions of the pentagonal {Mo(Mo₅)} building groups, cf. ref. [11]) statistically distributed over the 30 vertices of an icosidodecahedron. The acetate ligands are located inside the sphere and are coordinated in a bidentate fashion to the metal centers, preferentially bridging Fe and Mo sites. In crystals of **2** the icosahedral spherical building blocks, that is {Mo(Mo)₅}₁₂{Mo₆Fe}_{24}-type spheres,

[*] Prof. Dr. A. Müller, Dr. S. K. Das, Dipl.-Chem. M. O. Talismanova, Dr. H. Bögge, Dr. P. Kögerler, M. Schmidtman, Dipl.-Chem. S. S. Talismanov, E. Krickemeyer
Lehrstuhl für Anorganische Chemie I
Fakultät für Chemie, Universität Bielefeld
Postfach 100131, 33501 Bielefeld (Germany)
Fax: (+49) 521-106-6003
E-mail: a.mueller@uni-bielefeld.de
Dr. P. Kögerler, Prof. Dr. M. Luban
Ames Laboratory and Department of Physics and Astronomy
Iowa State University
Ames, IA 50011-3160 (USA)

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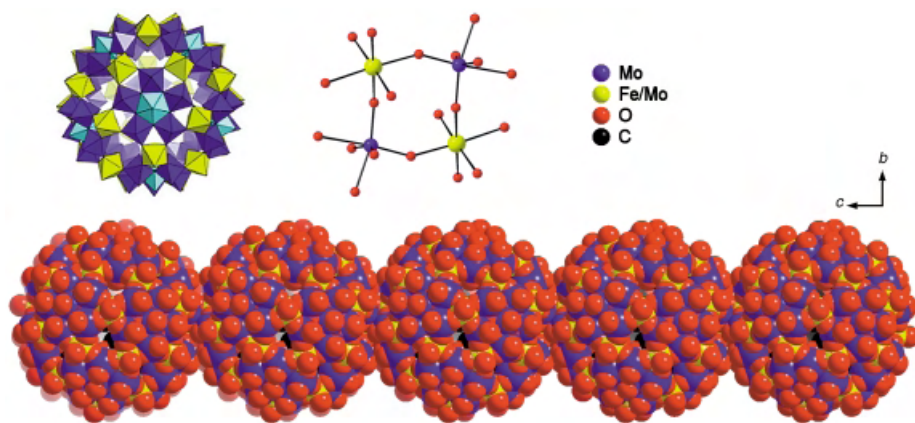
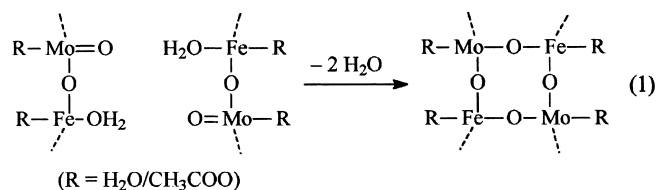


Figure 1. Representation of the structures of the discrete anion **1a** in crystals of **1** (polyhedra), of the anionic chain **2a** in crystals of **2** (space-filling with the option to identify the Mo positions), as well as of the linking area of the chain **2a** (ball-and-stick; bond lengths [Å] and angles [°] in the M_4O_4 ($M = \text{Mo/Fe}$) ring: Mo–O: 1.72/1.78; Fe–O: 1.96/1.98; Mo–O–Fe: 147.0/149.9; O–Mo–O: 101.5; O–Fe–O: 93.2).

are linked to form chains (Figure 1): Two neighboring spheres A and B are connected by a $\text{Mo}_A\text{--O--Fe}_B$ and a $\text{Fe}_A\text{--O--Mo}_B$ group, for which the two metal positions of each sphere (e.g., Fe_A and Mo_A) are connected by a μ -oxo-type center. This results in a nearly square Fe_2Mo_2 arrangement (Figure 1 top right), the center of which coincides with a crystallographic inversion center (see below for the type of mechanism). Interestingly, the geometric details of the Fe–O–Mo bridging group and the Fe–O–Mo motifs found in the spheres do not differ significantly ($\text{Mo}\cdots\text{Fe}$: ca. 3.6 Å). This has important implications for the magnetic properties as described below. The square-type linking group in **2** (Figure 1) is topologically equivalent to the type of linking found in dumbbell-shaped $\{\text{C}_{60}\}_2$ dimers, for which the linking region can be compared with a cyclobutane unit built up by two intra- and two inter-sphere C–C bonds.^[5c]

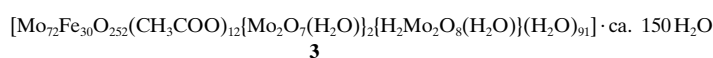
The formation of **2** is initiated by drying crystals of **1**, that is by the loss of crystal water and finally results in the condensation of the anionic cluster spheres so as to link the spheres as infinite chains through the above-described bridging motifs. This is caused by the fact that $\{\text{Fe}^{\text{III}}(\text{H}_2\text{O})_2\}^{3+}$ -type H_2O ligands are substituted by terminal Mo=O groups of $\{\text{Mo}(\text{Mo}_5)\}$ pentagons of neighboring spheres formally acting as ligands in accordance with Equation (1).

The driving force for the reaction is entropy gained by emission of water molecules. The initial loss of crystal water molecules causes decreasing inter-sphere distances, which leads to the situation that an Mo=O group formally acts as a ligand while replacing a H_2O group of an adjacent sphere as mentioned above. This S_N -type reaction initiated by an Mo=O group does not occur for the yellow neutral discrete $\{\text{Mo}^{\text{VI}}(\text{Mo}_5^{\text{VI}})\}_{12}\{\text{Fe}_3^{\text{III}}\}$ -type cluster found in **3**^[7] but in the present case due to the increase in electron density in **1a** at the



terminal Mo=O oxygen positions by the abundance of six (partially delocalized) 4d electrons which cause also the dark color. Remarkably the binuclear Mo_2^{VI} -type linkers of **3** (responsible for the neutrality of the cluster) are not abundant in **1** and **2** due to the different preparation method used here.

Interestingly, not only the crystallinity but also the space group ($P2_1/n$) is preserved throughout the solid-state reaction **1** $\rightarrow$ **2**. Comparing the packing of the spheres in the crystal lattice of **2** with that of **1** reveals that the distances between the $\{\text{Mo}(\text{Mo}_5)\}_{12}$ - $\{\text{Mo}_6\text{Fe}_{24}\}$ -type ball units shrink drastically in the direction of the crystallo-



graphic c axis (Figure 2): Correspondingly, the c axis of **2** is even 5.7 Å shorter than the corresponding one of **1** (see ref. [9]).

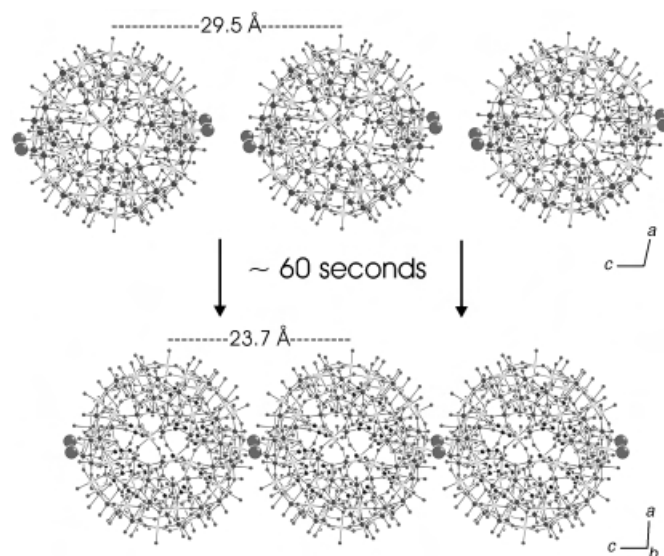


Figure 2. Schematic demonstration of the room-temperature solid-state reaction leading to the chain of **2** caused by linking the anionic spheres **1a**.

The magnetism of **2** can be best explained by comparing it with the prototypical case of the analogous discrete $\{\text{Mo}_2^{\text{VI}}\text{Fe}_{30}^{\text{III}}\}$ spheres of **3**,^[7] currently the largest molecular mesoscopic paramagnet.^[12] In both systems O–Mo–O groups mediate antiferromagnetic exchange between the near-perfect octahedrally coordinated $S = 5/2$ Fe^{III} centers (see also Mössbauer data). In the case of **3**, $\chi_{\text{mol}}T$ increases with T and at room temperature approaches the value expected for 30 uncorrelated $S = 5/2$ centers, namely 131.25 emu K mol^{-1} (spin-only for $g = 2.0$), while the room-temperature value of $\chi_{\text{mol}}T$ found for **2**, 104.0 emu K mol^{-1} , very nearly equates to the expected value for 24 uncorrelated $S = 5/2$ Fe^{III} centers, namely

105.0 emu K mol⁻¹.^[13] As the (partially) delocalized Mo(4d) electrons are, like in the reduced {Mo₁₀₂}-type Keplerate,^[11] strongly coupled and thus contribute only to a negligible extent to the overall magnetic moment, the high-temperature data indicate that in **2** six of the 30 Fe^{III} positions in **3** are occupied by (effectively) nonmagnetic centers. Down to low temperatures the measured susceptibility of both **2** and **3** (Figure 3) are in very good agreement with the Curie–Weiss function $\chi = C/(T - \Theta)$ but the derived Weiss temperatures

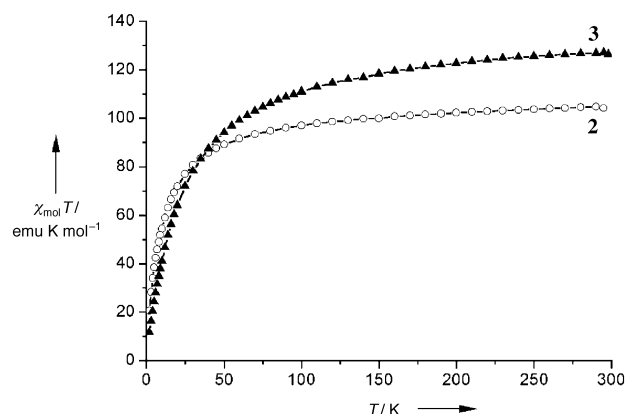


Figure 3. The temperature dependence of $\chi_{\text{mol}}T$ compared for **2** and **3**.

differ significantly ($\Theta(\mathbf{2}) = -13$ K, $\Theta(\mathbf{3}) = -21.6$ K, using susceptibility data extending from 20–300 K).^[12, 14a] The value of the ratio $\Theta(\mathbf{2})/\Theta(\mathbf{3})$ can be explained by adopting the following simple picture. The same single Heisenberg exchange constant J is assumed for the nearest neighbor Fe...Fe interactions in **2** and **3** since the geometrical parameters of the relevant Fe–O–Mo–O–Fe groups including the bridges between the spheres are virtually identical. It then follows that Θ is proportional to the absolute number of nearest neighbor Fe...Fe contacts per sphere,^[15] which in **2** is decreased in comparison to **3** by the introduction of six centers that are effectively not contributing to the paramagnetism, that is, (effectively) nonmagnetic. Assuming a uniform statistical distribution of these nonmagnetic centers over the 30 icosidodecahedron vertices results in 38 Fe...Fe contacts compared to the 62 contacts of a hypothetical all-iron configuration (60 icosidodecahedron edges and two distinct bridges to the adjoining spheres in the chain). We therefore obtain $\Theta(\mathbf{2}) = 38/62 \times \Theta(\mathbf{3}) = -13.2$ K, in excellent agreement with the experimentally determined value. It is noteworthy that, because the Weiss temperature reflects the ordering and the distribution of the nonmagnetic positions over all 30 possible positions, we are able to draw structural conclusions that cannot be obtained from the X-ray diffraction analysis or other analytical techniques.^[14b] Future investigations will center on the low-temperature/high-field regime. In particular, we will probe whether a highly symmetric frustrated ground-state configuration is achieved for **2** as occurs in compound **3**.^[12]

The results reported here focus on several interesting aspects. Nanosized spherical capsule-type objects get linked as one-dimensional chain structures in a room-temperature solid-state reaction, which can be regarded as a type of crystal

engineering process. Additionally, the capsule itself, that is the building block has interesting properties for materials science.^[3] Another important feature is that we deal with spherical capsules of the type (pentagon)₁₂(linker)₃₀ ($L = \text{Fe}(\text{H}_2\text{O})^{3+}$,^[7] $\text{MoO}(\text{H}_2\text{O})^{3+}$ ^[11]) where the linkers can be stepwise exchanged with the option of changing the surface properties for different purposes. For example, by changing appropriately the degree of electron density on the surface (that is, in the present case, by the number of $\text{MoO}(\text{H}_2\text{O})^{3+}$ groups), the nucleophilicity can correspondingly be increased thus, for instance, enabling different types of inter-sphere condensation reactions. The type of linking depends on the $\text{MoO}^{3+}/\text{Fe}^{\text{III}}$ ratio. Furthermore, there is an interesting electronic structure based on the two couples $\text{Fe}^{\text{II}}-\text{Mo}^{\text{VI}}$ and $\text{Fe}^{\text{III}}-\text{Mo}^{\text{V}}$ which have very close redox potentials. Therefore the actual type of electronic structure can lead to temperature-dependent electron transfer in anion **2a**.^[16, 17] Finally, the specific reaction type as well as the resulting products reported here are just one of a myriad of possibilities that appear achievable in future investigations with this system.

Experimental Section

1: $\text{FeCl}_2 \cdot 4 \text{H}_2\text{O}$ (0.5 g, 2.51 mmol) was added to a solution of $\text{Na}_2\text{MoO}_4 \cdot 2 \text{H}_2\text{O}$ (3.0 g, 12.40 mmol) in H_2O (25 mL) and CH_3COOH (100%; 10 mL). After acidification with 32% HCl (2.0 mL) the solution was stirred for 10 min at room temperature and the resulting blue solution was filtered from the blue precipitate and kept in a 100 mL Erlenmeyer flask at 20 °C. After one day, the solution was filtered again. The black crystals (plates or “rhombic” shaped prisms), precipitated after three days, were directly characterized while still wet by single-crystal X-ray structure analysis after they had been extracted from the mother liquor and cooled to liquid nitrogen temperature (otherwise these crystals tend to rapidly lose crystal water).

2: The wet crystals of **1** were filtered, washed with a small amount of cold water, and dried in argon at room temperature. The linking-type reaction based on drying with formation of the chain compound **2** is very fast. Yield: 0.14 g (10% based on Fe). Correct elemental analysis regarding all the elements; but as the Na and C content is very small and the Na^+ ions as well as the acetate groups are partially disordered an error limit regarding their numbers has to be taken into account, that is, a different composition showing, for example, one more Na^+ and acetate cannot be excluded. Characteristic IR bands (KBr pellet; 1800–500 cm⁻¹): $\tilde{\nu} = 1618$ (m, $\delta(\text{H}_2\text{O})$), 1541 (m, $\nu_{\text{as}}(\text{COO})$), 1420 (w-m, $\nu_s(\text{COO})$), 955 (m, $\nu(\text{Mo=O})$), 773 (s), 627 (w-m), 570 (s) cm⁻¹; characteristic resonance Raman bands (solid state; $\lambda_e = 1064$ nm, 1000–200 cm⁻¹): $\tilde{\nu} = 835$ (s), 633 (m), 463 (m-w) cm⁻¹; UV/Vis (solid-state reflectance spectrum, cellulose used as a white standard): $\lambda \approx 390$ (br), 580 (w, br), 850 (w, br), 1064 (w, br) nm; ⁵⁷Fe Mössbauer spectrum (77 K; isomer shift and quadrupole splitting characteristic for Fe^{III}O₆-type groups, in mm s⁻¹): $\delta = 0.52$, $\Delta E_Q = 0.77$.

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- [9] Crystal structure analysis for **1**: $C_{40}H_{528}Fe_{24}Mo_{78}Na_2O_{532}$, $M_r = 18394.1$ g mol $^{-1}$, monoclinic, space group $P2_1/n$, $a = 25.505(1)$, $b = 36.462(2)$, $c = 29.462(1)$ Å, $\beta = 103.556(1)^\circ$, $V = 26635(2)$ Å ^{3} , $Z = 2$, $\rho = 2.294$ g cm $^{-3}$, $\mu = 2.524$ mm $^{-1}$, $F(000) = 17892$, crystal size: $0.36 \times 0.16 \times 0.12$ mm ^{3} . Crystals of **1** were removed from the mother liquor and immediately cooled to 183(2) K on a Bruker AXS SMART diffractometer (three-circle goniometer with 1 K CCD detector, Mo K_{α} radiation, graphite monochromator; hemisphere data collection in ω at 0.3° scan width in three runs with 606, 435, and 230 frames ($\phi = 0, 88$ and 180°) at a detector distance of 5.0 cm). A total of 157370 reflections ($0.90 < \theta < 27.01^\circ$) were collected of which 57462 reflections were unique ($R(\text{int}) = 0.0632$). An empirical absorption correction using equivalent reflections was performed with the program SADABS. The structure was solved with the program SHELXS-97 and refined by using SHELXL-93 to $R = 0.0759$ for 34041 reflections with $I > 2\sigma(I)$, $R = 0.1398$ for all reflections; max./min. residual electron density 3.725 and -1.897 e Å $^{-3}$. Crystal structure analysis for **2**: $C_{40}H_{384}Fe_{24}Mo_{78}Na_2O_{460}$, $M_r = 17097.17$ g mol $^{-1}$, monoclinic, space group $P2_1/n$, $a = 25.360(1)$, $b = 36.647(1)$, $c = 23.730(1)$ Å, $\beta = 93.733(1)^\circ$, $V = 22007(2)$ Å ^{3} , $Z = 2$, $\rho = 2.580$ g cm $^{-3}$, $\mu = 3.032$ mm $^{-1}$, $F(000) = 16452$, crystal size: $0.16 \times 0.16 \times 0.04$ mm ^{3} . Dried crystals of **2** were cooled to 183(2) K on a Bruker AXS SMART diffractometer (three circle goniometer with 1 K CCD detector, Mo K_{α} radiation, graphite monochromator; hemisphere data collection in ω at 0.3° scan width in three runs with 606, 435, and 230 frames ($\phi = 0, 88$ and 180°) at a detector distance of 5.0 cm). A total of 112815 reflections ($0.98 < \theta < 25.01^\circ$) were collected of which 38737 reflections were unique ($R(\text{int}) = 0.0736$). An empirical absorption correction using equivalent reflections was performed with the program SADABS. The structure was solved with the program SHELXS-97 and refined by using SHELXL-93 to $R = 0.0622$ for 23168 reflections with $I > 2\sigma(I)$, $R = 0.1231$ for all reflections; max./min. residual electron density 3.064 and -1.414 e Å $^{-3}$. (SHELXS/L, SADABS from G. M. Sheldrick, University of Göttingen 1993/97; structure graphics with DIAMOND 2.1 from K. Brandenburg, Crystal Impact GbR, 2001.) CCDC-169551 (**1**) and CCDC-169552 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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- [13] Susceptibility measurements were performed from 2–300 K at 0.5 Tesla using a Quantum Design MPMS-5S and a MPMS-2 SQUID magnetometer.
- [14] a) The nearly perfect agreement with the Curie–Weiss law also rules out the presence of Fe^{II} centers which would result in a significant deviation from the linearity of $1/\chi$ versus T due to temperature-dependent spin-orbit coupling contributions (see, e.g., H. Lueken, *Magnetochemie*, Teubner, Stuttgart **1999**, pp. 246–257). b) It is interesting to compare the present situation of a uniform distribution of (effectively) nonmagnetic positions with other distribution scenarios, for example, maximum clustering of these positions (i.e., all are situated on neighboring sites of the icosidodecahedron), for which the Weiss temperature should change to -18 K. Here, the excellent fit provided by the Curie–Weiss expression in addition indicates the uniform character of the individual spheres with respect to the ratio of the number of magnetic to (effectively) nonmagnetic positions (24:6), whereas a distribution of different ratios with the same average 24:6 ratio would not be accurately characterized by a Curie–Weiss term. By single-crystal X-ray structure analysis it would not be possible to discriminate between the situation of all spherical units having the same composition as in the present case and the situation of the abundance of spheres with different ratios of the magnetic/effectively nonmagnetic linkers but yielding overall the same Fe^{III}/Mo^V average ratio of 24:6.
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Noninterpenetrating Square-Grid Coordination Polymers With Dimensions of $25 \times 25 \text{ \AA}^2$ Prepared by Using N,N' -Type Ligands: The First Chiral Square-Grid Coordination Polymer**

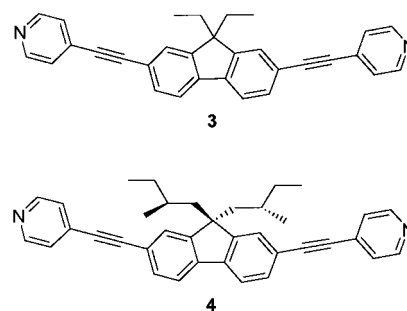
Neil G. Pschirer, Delia M. Ciurtin, Mark D. Smith, Uwe H. F. Bunz,* and Hans-Conrad zur Loye*

Self-assembled coordination polymers with well-defined channels or pores have attracted intense interest as microporous frameworks in which to carry out spatially confined reactions that are potentially catalyzed by functional appendages projecting to the inside of a framework structure.^[1–8] Accordingly, noninterpenetrating square-grid (or rectangular-grid) polymers are an important class of networks that have predictable openings and can accommodate guest molecules that meet size-exclusion criteria.^[9, 10] A challenge has been to modify such square-grid polymers through the incorporation of chiral moieties and allow their use in chiral recognition applications.

A large number of square-grid polymers are known, which were initially based on cyano ligands, and more recently have been based on N,N' -bipyridine-type ligands.^[11] Many of these form interpenetrating frameworks that preclude their use as porous materials. There are, however, a fair number of noninterpenetrating square-grid coordination polymers, and Zaworotko recently classified their structures based on the stacking of the grids.^[11] N,N' -bipyridine-type ligands are convenient linkers for achieving square-grid architectures with predictable grid dimensions, as demonstrated by Fujita et al. using 4,4'-bipyridine (**1**) to form $[[[\text{Cd}(\text{1})_2(\text{H}_2\text{O})_2](\text{NO}_3)_2]_n]$. More recently the longer 4,4'-bis(4-pyridyl)biphenyl (**2**) ligand in $[[[\text{Ni}(\text{2})_2(\text{NO}_3)_2] \cdot 4 o\text{-xylene}]_n]$ was reported by the same group. The latter polymer, for example, had grid dimensions of $20 \times 20 \text{ \AA}^2$, making it the largest at that time.^[12] The stacking of the grids, in the case of noninterpenetrating frameworks, further determines the maximum accessible channel size that can be achieved in such systems. While it has been suggested, based on existing systems, that longer ligands will favor the formation of interpenetrating over noninterpenetrating grid structures,^[13] it appears that the attachment of side chains that project perpendicular from the linker, can inhibit interpenetration and enable the formation of large square grids with infinite channels.^[14]

An important issue in such noninterpenetrating square-grid systems is to achieve control over the size of the channels, which can be effected by using two N,N' -bipyridine ligands of

different lengths^[9] or by modifying the ligand to effect the shape of the grid. We decided to employ the latter strategy and modified the ligand to gain control over the physical dimensions of the grid and, more importantly, gain control over the internal chemistry of the channels. Herein, we report the synthesis^[15] of two new types of very long, N,N' -bipyridine-based ligands containing side chains that project perpendicular to the linking direction: 9,9-diethyl-2,7-bis(4-pyridylethynyl)fluorene (**3**), and chiral 9,9-bis[(*S*)-2-methylbutyl]-2,7-bis(4-pyridylethynyl)fluorene (**4**), and their use in the formation of noninterpenetrating square-grid polymers containing chiral and nonchiral chemical environments in large channels. Treatment of **3** or **4** with copper nitrate in ethanol leads to exceptionally large, noninterpenetrating, square-grid polymers with grid dimensions of $25 \times 25 \text{ \AA}^2$.



Single crystals of $[\text{Cu}(\text{3})_2(\text{NO}_3)_2]$ (**5**) were grown by carefully layering a solution of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (8.0 mg, 0.033 mmol) in ethanol (1.65 mL) onto a solution of **3** (28.0 mg, 0.066 mmol) dissolved in dichloromethane (2.0 mL). Crystals of $[\text{Cu}(\text{4})_2(\text{NO}_3)_2]$ (**6**) were grown using a similar procedure: $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (6.0 mg, 0.025 mmol) was dissolved in ethanol (1.0 mL) and the solution was layered onto **4** (24.8 mg, 0.05 mmol) dissolved in dichloromethane (2.0 mL); crystals were obtained after two days.

The noninterpenetrating square-grid structure of **5** is depicted in Figure 1 a.^[16] The short side chains of the ligand lead to an open-grid space, in particular as the ligand orientation alternates with the fluorene group rotated by approximately 90° on opposing sides of each grid, projecting the side chains parallel and perpendicular to the plane of the grid. The grid dimension is $25 \times 25 \text{ \AA}^2$, making it, we believe, the largest known noninterpenetrating grid to date. While interpenetrating square-grid polymers are typically nonporous since all available space is filled by the interpenetration, even large noninterpenetrating square-grid polymers, such as the above-mentioned $[[[\text{Ni}(\text{2})_2(\text{NO}_3)_2] \cdot 4 o\text{-xylene}]_n]$ can have reduced porosity due to the stacking of the grids; in which case the $20 \times 20 \text{ \AA}^2$ openings are reduced to $10 \times 20 \text{ \AA}^2$. In the case of **5** the ABAB stacking of the layers (Figure 1 b; B-type grid^[11]) generates reduced, yet still very large infinite channels of dimensions $16 \times 16 \text{ \AA}^2$. The solvent-accessible volume calculated with the PLATON program^[17] is $5115.1 \text{ \AA}^3$, or 54.1 % of the volume of the unit cell. Although not filled by the side chains, the channels are occupied by a sea of disordered solvent molecules and nitrate anions, which could not be defined crystallographically. A view parallel to four

[*] Prof. Dr. U. H. F. Bunz, Prof. Dr. H.-C. zur Loye, N. G. Pschirer, D. M. Ciurtin, Dr. M. D. Smith
Department of Chemistry and Biochemistry
University of South Carolina
Columbia, SC 29208 (USA)
Fax: (+1) 803-777-8508
E-mail: bunz@mail.chem.sc.edu, zurloye@sc.edu

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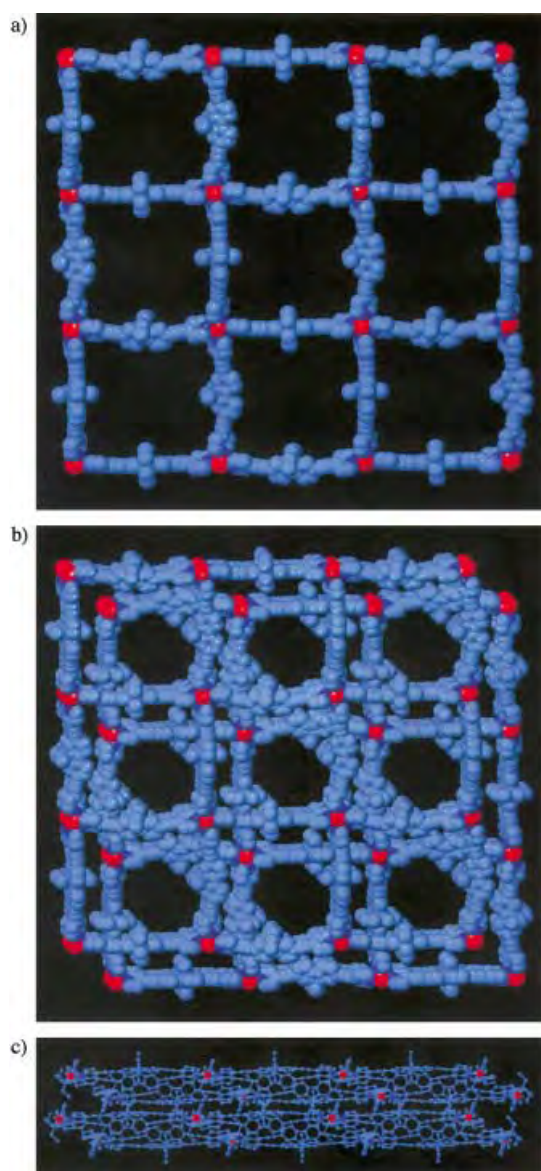


Figure 1. a) Single square-grid layer of $[\text{Cu}(\mathbf{3})_2(\text{NO}_3)_2]$ (**5**). The fluorene group is rotated by approximately 90° on opposing sides of each grid, projecting the side chains parallel and perpendicular to the plane of the grid. The ligand is shown in blue and the copper atoms in red. b) Stack of four square-grid layers. The grids stack in an ABAB fashion, creating large infinite channels of dimensions $16 \times 16 \text{ \AA}^2$. c) A view parallel to four adjacent stacked grids shows that the grids are virtually planar.

adjacent stacked grids (Figure 1c) shows that the grids are virtually planar.

The major accomplishment using these fluorene-based ligands, however, is the formation of the chiral system **6** (space group $P2_1$), using the chiral ligand **4**. There are several strategies to generate chiral systems: 1) starting with the use of achiral components to make chiral structures,^[18–20] 2) the use of chiral ligands in molecular squares and their aggregation into chiral clusters,^[21] and 3) the use of helical chains^[22] or helical frameworks;^[23–25] the work described herein extends the concept of chiral molecular square complexes, assembled by using chiral ligands, to polymeric structures and, to the best of our knowledge, **6** is the first chiral noninterpenetrating square-grid coordination polymer.

The structure of the grid of **6** is shown in Figure 2a, and the ABCABC stacking of the layers in Figure 2b. In **6**, by contrast with **5**, the fluorene groups maintain the same orientation on all grid sides. This forces the R groups to project into the grid, thus taking up more space than in **5** and thereby significantly reducing the channel size. The grid dimension is still $25 \times 25 \text{ \AA}^2$; however, the ABCABC stacking significantly reduces the accessible channel dimension to about $8 \times 8 \text{ \AA}$, which is also reflected in a greatly diminished solvent-accessible volume of $423.2 \text{ \AA}^3$ (11.8% total unit cell volume) compared to **5**. Unlike **5**, the grid plane of **6** is not planar and in Figure 2c the undulation can be clearly seen.

The existence of this chiral and porous system suggests future opportunities for chiral selectivity of host molecules

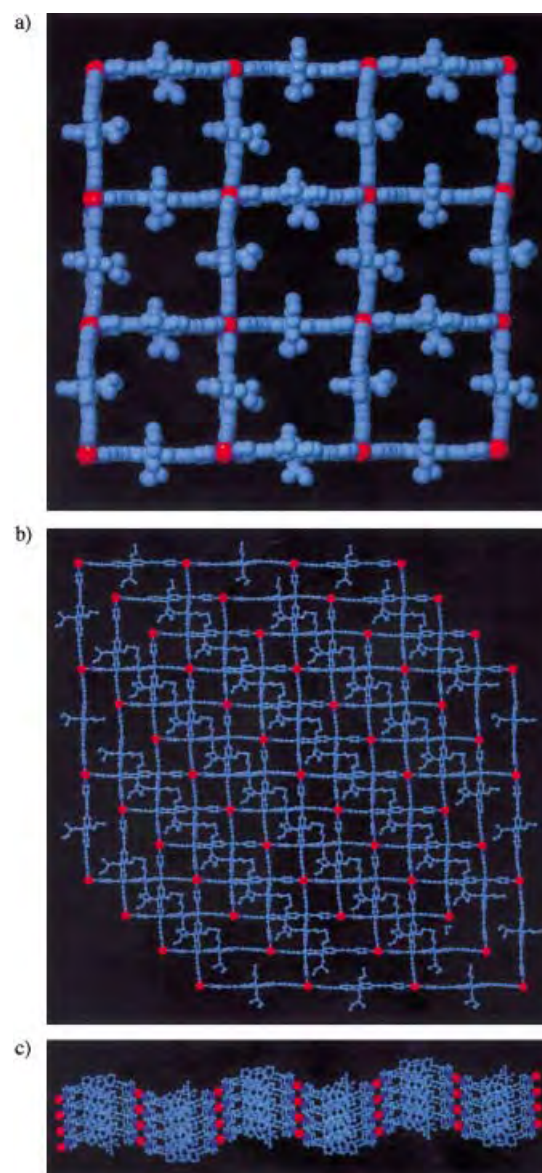


Figure 2. a) Single square-grid layer of $[\text{Cu}(\mathbf{4})_2(\text{NO}_3)_2]$ (**6**). The fluorene groups maintain the same orientation on all grid sides, forcing the side chains to project into the grid. b) Stack of four square-grid layers. The grids stack in an ABCABC fashion, creating infinite channels of dimensions $8 \times 8 \text{ \AA}^2$. c) A view parallel to four adjacent stacked grids shows that the grids are not planar but undulate.

and even, potentially, chiral-selectivity for reactions that might benefit from taking place inside spatially confined channels and its local chemical environment. The use of the new ligand **4** represents a proof-of-concept in this respect, as we have generated the new *noninterpenetrating* grid **6**, in which the organic side chains project inward. This illustrates an exciting aspect of this square-grid family, namely that it can potentially be further modified to be functional and space-specific. That is, by using different polar or nonpolar groups, the amount of space in the channel should be controllable—while the noninterpenetrating square-grid frameworks are maintained. One can readily envision their use for size-exclusion chemistry, for reactions that are promoted by reactant proximity,^[3, 4] and for those catalyzed by the local chemical environment. Work towards these goals is underway and will be reported in the near future.

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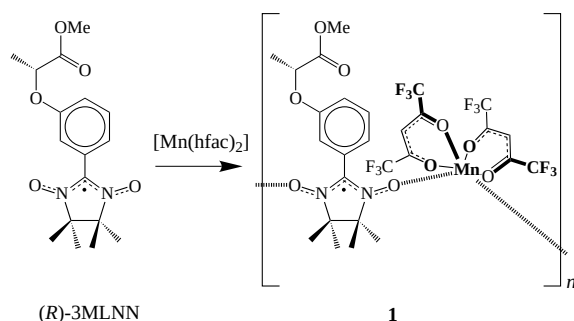
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- [15] **3**: 9,9-Diethyl-2,7-diethynylfluorene (0.26 g, 0.96 mmol), 4-bromopyridine hydrochloride (0.47 g, 2.40 mmol), [Pd(PPh₃)₂Cl₂] (0.05 g, 0.07 mmol), CuI (0.14 g, 0.072 mmol), and PPh₃ (0.50 g, 0.01 mmol) were dissolved in triethylamine (20 mL) in a dry Schlenk flask thoroughly flushed with nitrogen, and heated to 70 °C for 24 h. After aqueous workup and column chromatography (CH₂Cl₂/MeOH), **3** (0.39 g, 96 %) was isolated as a yellow powder: m.p. 191–194; ¹H NMR (CDCl₃): δ = 8.60 (dd, 4H, J = 1.7, 4.7 Hz), 7.70 (d, 2H, J = 7.7 Hz), 7.54 (d, 2H, J = 8.0 Hz), 7.52 (s, 2H), 7.39 (dd, 4H, J = 1.7, 4.4 Hz), 2.06 (q, J = 7.1 Hz, 4H), 0.32 (t, J = 7.1 Hz); ¹³C NMR: δ = 150.3, 149.6, 141.5, 132.0, 131.9, 131.4, 131.1, 128.4, 128.3, 126.2, 125.3, 120.9, 120.1, 94.8, 87.1, 56.3, 32.5, 8.3. **4**: 9,9-Bis[(S)-2-methylbutyl]-2,7-di(trimethylsilyl)ethynylfluorene (2.00 g, 5.23 mmol) and 4-bromopyridine hydrochloride (3.05 g, 15.68 mmol) were dissolved in triethylamine (10 mL) in a dry Schlenk flask thoroughly flushed with nitrogen. KOH/EtOH solution (10 % solution; 10 mL) was then added followed by the addition of [Pd(PPh₃)₂Cl₂] (0.08 g, 0.11 mmol), CuI (0.03 g, 0.16 mmol), and PPh₃ (0.08 g, 0.30 mmol). The flask was once again flushed with nitrogen then heated to 70 °C for 14 h. After aqueous workup and column chromatography (CH₂Cl₂/MeOH), the product **4** (1.05 g, 39 %) was isolated as a pale yellow powder: m.p. 173–175; ¹H NMR (CDCl₃): δ = 8.60 (d, 4H, J = 5.0 Hz), 7.70 (d, 2H, J = 8.4 Hz), 7.58–7.51 (m, 4H), 7.41 (d, J = 5.7 Hz), 2.14–2.07 (m, 2H), 1.93–1.86 (m, 2H), 0.94–0.75 (m, 4H), 0.58 (dd, 8H, J = 14.8, 7.3 Hz), 0.26 (dd, 6H, J = 15.6, 6.8 Hz); ¹³C NMR (CHCl₃): δ = 151.7, 151.4, 151.0, 149.6, 141.4, 141.3, 131.7, 131.2, 127.4, 127.2, 127.0, 120.5, 120.2, 95.1, 87.0, 54.9, 54.8, 47.9, 47.8, 31.1, 30.9, 30.7, 30.6, 20.9, 20.8, 10.9, 10.8.
- [16] Crystal data **5**: Cu(C₃₀H₂₄N₂)₂(NO₃)₂(solvent)_x; M_r = 992.61, rectangular green bar, dimensions 0.40 × 0.20 × 0.18 mm³, monoclinic, P2₁/c, a = 33.373(3), b = 33.578(3), c = 8.5066(9) Å, β = 97.029(3)°, V = 9461.0(2) Å³, Z = 4. Intensity data covering a hemisphere of reciprocal space measured (ω scan mode) to 2θ_{max} = 50.1° with a Bruker SMART APEX CCD diffractometer (MoK_α radiation, λ = 0.71073 Å), at 293(2) K. A total of 55524 reflections collected; 16730 independent, 6324 with I > 2σ(I). Lorentzian polarization and absorption corrections applied (SADABS, μ = 0.260 mm⁻¹, T_{max}/T_{min} = 0.980/0.856). Structure solved with direct methods; refined against F² using all data (SHELXTL version 5.1): R1 = 0.0541, wR2 = 0.1338 (I > 2σ(I)). The sea of diffusely scattering solvent accounted for with the SQUEEZE program (solvent-accessible void volume = 5115 Å³, or 1407 e⁻/cell).^[17] The final ρ_{calcd}, F(000), and M_r reflect known contents only. Crystal data **6**: Cu(C₃₇H₃₆N₂)₂(NO₃)₂(CH₂Cl₂) · 2(C₂H₅OH), M_r = 1381.98, green plate, dimensions 0.22 × 0.12 × 0.03 mm³, monoclinic, P2₁, a = 10.432(3), b = 31.631(9), c = 10.910(3) Å, β = 96.126(6)°, V = 3579.6(2) Å³, Z = 2. Intensity data covering a hemisphere of reciprocal space measured (ω scan mode) to 2θ_{max} = 45.4° with a Bruker SMART APEX CCD diffractometer (MoK_α radiation, λ = 0.71073 Å) at 173(2) K. A total of 16560 reflections collected; 9462 independent, 2408 with I > 2σ(I). Lorentzian polarization correction applied; no absorption correction (μ = 0.44 mm⁻¹). Structure solved with direct methods; refined against F² using all data (SHELXTL version 5.1): R1 = 0.0700, wR2 = 0.1184 (I > 2σ(I)).
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An Enantiopure Molecular Ferromagnet**

Maria Minguet, Dominique Luneau,* Elsa Lhotel, Vincent Villar, Carley Paulsen, David B. Amabilino, and Jaume Veciana*

The importance that the presence of chirality—resulting from the presence of atomic stereogenic centers or atropisomeric conformations—may have in the behavior of molecular magnetic materials is an open question of great current interest.^[1] This interest has been encouraged by the observation of magneto–chiral effects,^[2] although other upshots of chirality as a result of symmetry breaking may be possible.

In an effort to unveil some of these possible influences, we initially focused on the synthesis of purely organic chiral α -nitronyl nitroxides,^[3] of which (*R*)-3MLNN (Scheme 1) is one.^[4] Here, we report the preparation and optical and magnetic properties of the coordination compound **1**, comprised of this radical and manganese(II) bis(hexafluoroacetylacetonate) ([Mn(hfac)₂]).



Scheme 1. Preparation of the complex **1**.

We were drawn to metallo–organic molecular magnetic materials^[5] because of: 1) their relatively high magnetic ordering temperatures compared with their organic counterparts,^[6] 2) their rich variety of chiral coordination modes,^[7] and 3) the anisotropy of the magnetic moments associated with the metal ions that could favor the observation of magneto–optical effects.^[2] The Mn(hfac)₂ nitronyl nitroxide

complexes are known in a variety of guises^[8] which include helical chains in a complex which crystallizes in a chiral space group, with spontaneous resolution of enantiomorphic crystals, and magnetic ordering.^[9] In addition, complexation of the same metal complex by a chiral bisnitroxide led to the formation of a metamagnet.^[10] The crystalline enantiopure chiral complex **1** reported here has homochirality as well as a ferromagnetic phase transition at 3 K. Below the transition temperature, intriguing dynamic behavior is observed culminating in the opening up of hysteresis loops below 800 mK. An explanation of this phenomenon is domain-wall pinning and depinning. Another interesting result is the observation of a magnetic avalanche phenomenon below 0.3 K.

The crystalline complex **1** (Scheme 1) exists as a coordination polymer in which each oxygen atom of the ONCNO unit of the radical coordinates to the paramagnetic metal ion in a *cis* manner (Figure 1a). The metal ion centers have the *A* configuration, or minus (*M*) helicity. The molecular conformation of the radical component in the complex is remarkably similar to the pseudo-eclipsed one present in crystals of the pure organic ligand, which crystallizes in the same chiral space group (*P*2₁2₁2₁).^[11] The polymeric chains run along the *b* axis (Figures 1b and 1c), with a distance

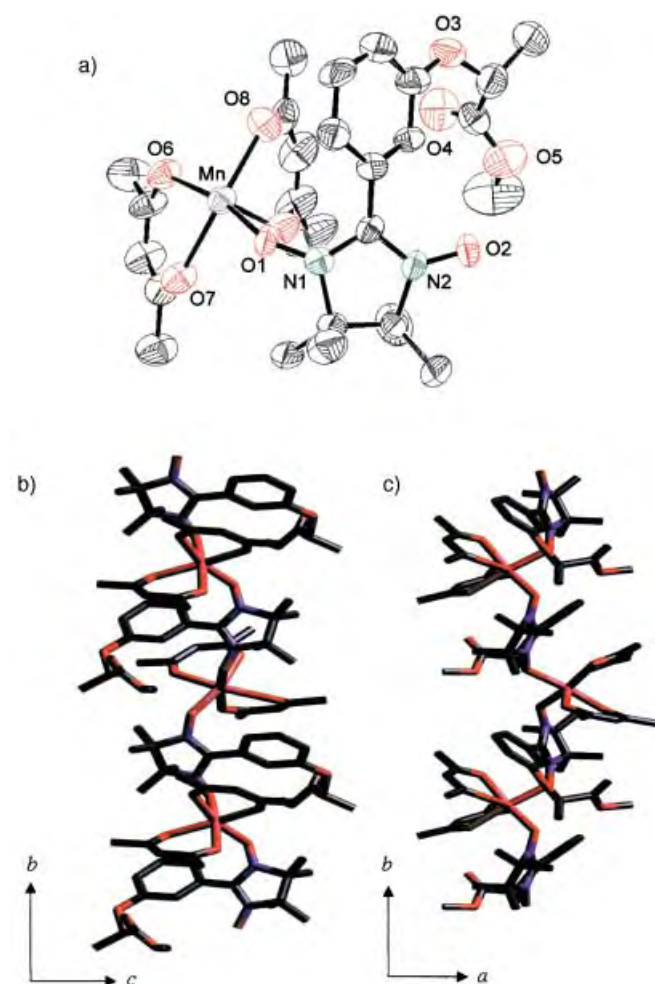


Figure 1. The crystal structure of **1**: a) An ORTEP view^[15] of the monomeric unit; cylindrical representations of b) the homochiral chains in the *a* plane and c) in the *c* plane (hydrogen and fluorine atoms omitted for clarity).

[*] Prof. J. Veciana, Dr. M. Minguet, Dr. D. B. Amabilino
Institut de Ciència de Materials de Barcelona (CSIC)
Campus Universitari
08193-Bellaterra (Spain)
Fax: (+34)93-580-5729
E-mail: vecianaj@icmab.es

Dr. D. Luneau
Service de Chimie Inorganique et Biologique (UMR 5046)
Département de Recherche Fondamentale sur la Matière Condensée
CEA-Grenoble, 38054-Grenoble (France)

Dr. C. Paulsen, V. Villar, E. Lhotel
Centre de Recherche sur les Très Basses Températures (UPR 5001)
CNRS, 25 avenue des Martyrs
38054-Grenoble Cedex 9 (France)

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between Mn^{II} ions within the chains of 7.57 Å. There are very short distances (3.30 and 3.43 Å) between the phenyl rings of the radical ligand and the CO group of the hfac ligands, consistent with π - π interactions, which may play an important role in determining the structure of the polymeric chain.^[9] The chains pack in a parallel manner such that each one is surrounded by six neighboring chains some of which are related by a screw-axis. The shortest inter-chain distances are between fluorine atoms of the CF₃ groups and CH groups from the two ligands (the six closest metal ion to metal ion distances are in the range 11.33–12.54 Å).

The UV/Vis absorption spectra of the complex **1**, recorded in KBr matrix, shows a longer wavelength visible absorption than the pure radical. This shift in the absorption is mirrored by changes in the optical activity of the complex, which was confirmed by performing circular dichroism (CD) spectroscopy of the ground crystals, also in KBr matrix (Figure 2).^[11] The Cotton effects displayed by the complex are as intense as those of the radical except for that at the longest wavelength. The significant positive effect at approximately 460 nm is particularly interesting for the possible observation of magneto-chiral effects, given the higher natural CD asymmetry factor ($g_{\text{NCD}} = 2(\epsilon_- - \epsilon_+)/(\epsilon_- + \epsilon_+) = \Delta\epsilon/\epsilon$) than the ligand.

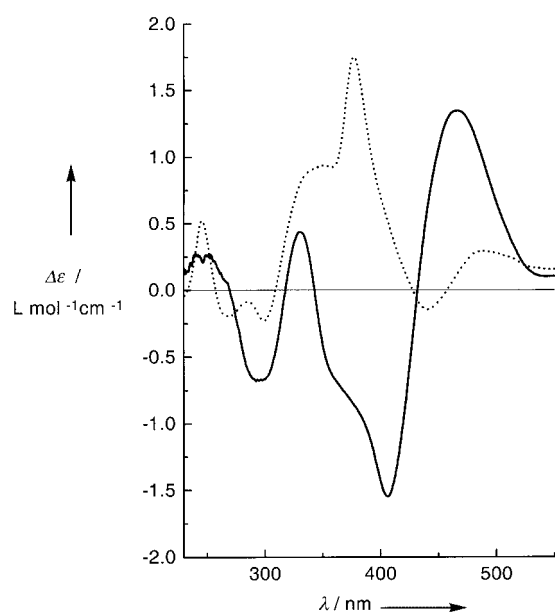


Figure 2. Solid state CD spectra of (R)-3MLNN (••••) and (R)-**1** (—) in KBr.

The temperature dependence of the molar magnetic susceptibility χ_m of a ground crystalline sample of **1** (measured in the temperature range from 2 to 350 K, Figure 3) shows a continuous increase of $\chi_m T$ upon cooling down to 3 K, from a value $\chi_m T = 5.6 \text{ cm}^3 \text{ K mol}^{-1}$ at 350 K, to very high values at low temperatures. Moreover, $\chi_m T$ shows a maximum at approximately 3 K, and decreases at lower temperatures. The increase of $\chi_m T$ upon cooling is the typical behavior of polymeric Mn(hfac)₂ nitronyl nitroxide complexes, which behave normally as one-dimensional (1D) Heisenberg ferromagnets, in which the non-compensation of the isotropic spins of the Mn^{II} ion ($S = 5/2$) and of the radical ($S = 1/2$) leads to an

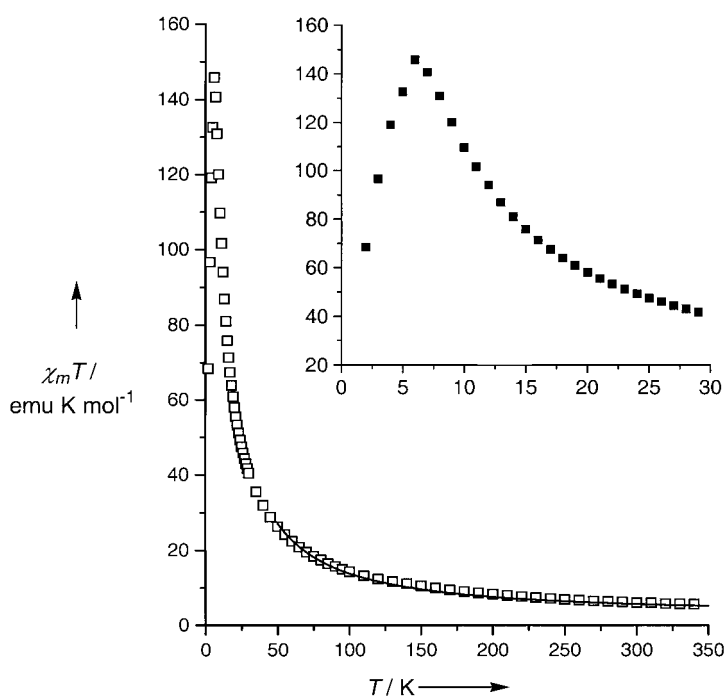


Figure 3. Temperature dependence of $\chi_m T$ versus T for a ground crystalline sample of (R)-**1**. The measurements were taken in a field of 100 Oe. The continuous line is the fit of experimental data ($\square$) above 50 K to the Seiden model. Inset: Expansion of the low-temperature region showing the maximum in $\chi_m T$.

increasing magnetic moment as the correlation length increases upon lowering the temperature. Fitting of the experimental data above 50 K to the Seiden model^[12] gives a J value (exchange coupling between $S = 1/2$ and $S = 5/2$ units) of -105 cm^{-1} with a fixed $g = 2$ value ($H = -2JS_1S_2$). This value is in the range of previous ones found in this type of Mn(hfac)₂ nitronyl nitroxide complex.^[8,9] The presence of a maximum of $\chi_m T$ at low temperatures suggests that the already correlated spins within each chain order magnetically between the chains.

To investigate the possibility of a phase transition near 3 K, low-temperature alternating current (ac) susceptibility and direct current (dc) magnetization measurements were made using the low-temperature high-field superconducting quantum interference device (SQUID) magnetometer developed at the CRTBT/CNRS in Grenoble. Figure 4 shows ac susceptibility data as well as the zero-field cooled (ZFC) and field cooled (FC) dc susceptibility. The peak in the real part (χ') of the ac susceptibility at a Curie temperature (T_c) of 3 K, along with a small frequency-independent signal in the imaginary part (χ'') of the ac susceptibility is the signature of a ferromagnetic phase transition and the onset of three-dimensional (3D) long-range magnetic order. The very large value of the susceptibility $\chi' = 1.0 \text{ emu cm}^{-3}$ at the peak corresponds to a demagnetization factor of $1/\chi' = N = 1$, a reasonable value for the elongated shape of the sample. At temperatures between 30 K to approximately 6 K the susceptibility data can be reasonably well fit to the formula $\chi = (C/T)\exp(2J/kT)$ which is predicted for a 1D Ising spin chain and implies $T_c = 0$. Note that the use of this formula is justified by the presence of a uni-axial anisotropy observed at low temperature (see

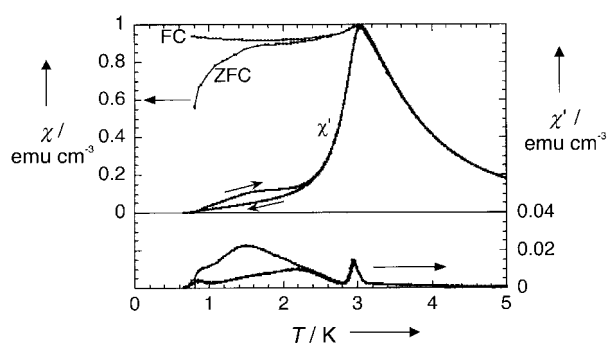


Figure 4. The real (χ') and imaginary (χ'') part of the ac susceptibility measured at 2.1 Hz in an ac field strength of approximately 0.1 Oe (bottom) and the zero-field cooled and field cooled dc susceptibility measured in a field of approximately 1 Oe (top). The measurements were made on an oriented small ($4 \times 0.9 \times 0.4$ mm) single crystal of mass 1.08 mg with the field aligned along the b axis (long direction) of the sample.

below). Near 6 K there is a crossover from the high-temperature 1D short-range correlations to 3D long-range ordering at T_c . Indeed after corrections for demagnetization effects the data can be scaled from approximately 5.5 K to T_c as $\chi = (T - T_c)^{-\gamma}$, and we find a value for the critical exponent $\gamma \approx 1.4$.

Below T_c nontrivial dynamic effects are observed. In particular from just below T_c to approximately 1 K, the ac susceptibility is highly nonlinear, depends strongly on the presence of (small) superimposed dc fields, is hysteretic in temperature, and above all is frequency dependent. Between approximately 1 and 0.6 K, χ' falls to zero, and a small but easily identifiable peak in χ'' is observed. Figure 5 shows the frequency dependence of the position of this peak, a straight line on this plot corresponds to a simple thermal activation law $\tau = \tau_0 \exp(E_b/k_B T)$ with $\tau_0 \approx 6 \times 10^{-11}$ s and where $E_b \approx 16$ K is an average activation energy barrier.^[13]

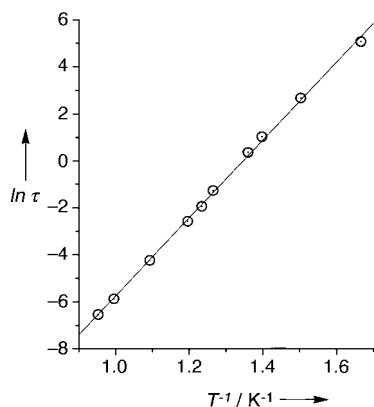


Figure 5. The frequency (f) dependence of the peak position in χ'' (observed near 1 K) for 0.001 to 180 Hz plotted as $\ln \tau$ versus $1/T$ where $\tau = 1/2\pi f$.

Associated with the increase in relaxation times as the temperature decreases and the abrupt decrease in χ'' below 1 K are the opening up of hysteresis loops (Figure 6). These data have been taken with a field step of 10 Oe, and with three measurements at each field. There is a small relaxation of the magnetization during the measurement of the hysteresis. Note that at 135 mK, the width of the loop is smaller than at

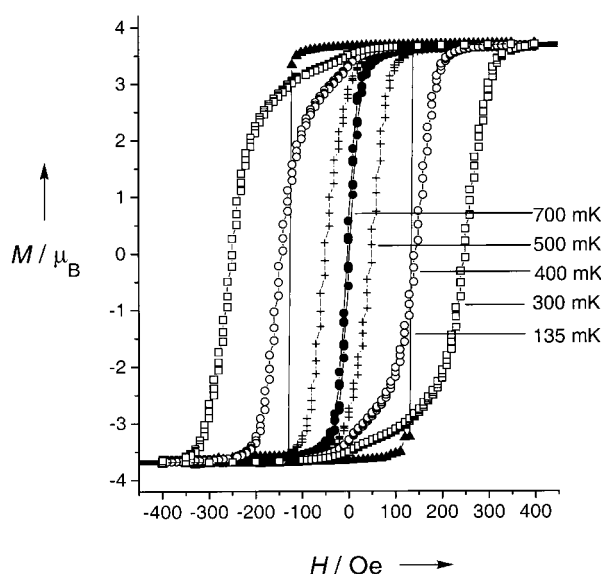


Figure 6. Opening up of hysteresis loops below 1 K showing the magnetic avalanche phenomenon.

300 mK! At this temperature, an avalanche of the magnetization is observed similar to those reported for the molecular cluster system $[\text{Mn}_{12}\text{O}_{12}(\text{O}_2\text{CCH}_3)_{16}(\text{H}_2\text{O})_4]$.^[14] At a certain value of applied field, there is an abrupt switching of a population ΔM of spins (i.e. as a result of domain wall depinning), which releases an energy $2\Delta M B_{\text{int}}$ as local heating (B_{int} is the internal field). This heat in turn helps push more spins over the top of the thermal activation barrier, which creates more heat and so on resulting in the magnetic equivalent of an avalanche. Indeed, a temperature pulse is observed just after the avalanche.

At fields greater than approximately 1 Tesla the magnetization eventually saturates at a value of $4\mu_B$, which corresponds to an $S = 2$ spin ground state for the Mn^{II} radical unit. This result therefore confirms the strong antiferromagnetic coupling of the manganese(II) ions ($S = 5/2$) with the radicals ($S = 1/2$) along the chain. Finally, low-temperature magnetization measurements along the a and c axis were also made. M versus H for these directions indicate the existence of a relatively strong uni-axial anisotropy, with the easy axis (the direction along which the spins orient preferentially) aligned along the spin chain (b axis) direction. Such results were independently confirmed by oriented single-crystal ESR experiments at low temperatures.

The unusual dynamic behavior can be explained in terms of simple domain-wall motion. At T_c , domains are created with perhaps a long-laminar form along the easy axis of the crystal. Near T_c the walls are soft, and the energy is high enough so that the walls can be displaced easily, and thus the ac susceptibility remains large. As the temperature decrease, the domain walls become more rigid, and their displacement becomes increasingly hindered by defaults or pinning on the surface with characteristic energy of the order 16 K. Below 1 K, relaxation by thermal activation becomes very slow, and hysteresis loops can be measured, and as a result, the ac susceptibility decreases to near zero. The unusual dynamic effects, as well as the existence of the uni-axial magnetic

anisotropy, may be a result of the special asymmetry of this enantiopure molecular magnet. We are presently performing experiments to probe the origin of such results as well as investigating the magneto-optic properties of this intriguing material.

Experimental Section

1: (*R*)-Methyl[3-(4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazolyl-1-oxy-3-oxide) phenoxy]-2-propionate ((*R*)-3MLNN (50 mg, 0.15 mmol), ref.[4]) in CH₂Cl₂ (20 mL) was added to a warm heptane (20 mL) solution of manganese(II) bis(hexafluoroacetylacetonate) (70 mg, 0.15 mmol) and the mixture was allowed to cool to room temperature. Upon standing green needles of **1** (55 mg, 45%) crystallized. The complex gave satisfactory elemental, mass spectrometry, and IR spectroscopic analysis. Crystal data for **1** C₂₇H₂₅F₁₂MnN₂O₉, *M* = 804.43, orthorhombic, space group *P*2₁2₁2₁, *a* = 12.022(4), *b* = 14.219(5), *c* = 20.294(7) Å, *α* = *β* = *γ* = 90°, *U* = 3469.2(19) Å³, *Z* = 4, *ρ* = 1.540 g cm⁻³, *μ* = 0.495 cm⁻¹, *F*(000) = 1624, 3994 measured reflections, 2981 unique reflections, collected on a Bruker P4 diffractometer with monochromatic MoK_α radiation (*λ* = 0.71073 Å). Number of parameters 460 for 3994 independent reflections with *I* > 2σ(*I*); solution SHELXS-97 (Sheldrick, 1990), refinement SHELXL-97 (Sheldrick, 1997), final *R* indices [*I* > 2σ(*I*)] *R* = 0.0801, *R*_w = 0.1941. Weighted *R*-factors *R*_w and all goodness-of-fit *S* are based on *F*². CCDC-158455 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

Magnetic measurements were performed on crystalline samples of the complex. The temperature dependence of the magnetic susceptibility in the range 2–350 K was measured in a field of 500 G using a Quantum Design SQUID magnetometer. The low-temperature measurements below 7 K were made using a high-field SQUID magnetometer developed at CRTBT/CNRS.

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The First Polymer-Supported and Recyclable Chiral Catalyst for Enantioselective Olefin Metathesis**

Kai C. Hultsch, Jesper A. Jernelius, Amir H. Hoveyda,* and Richard R. Schrock*

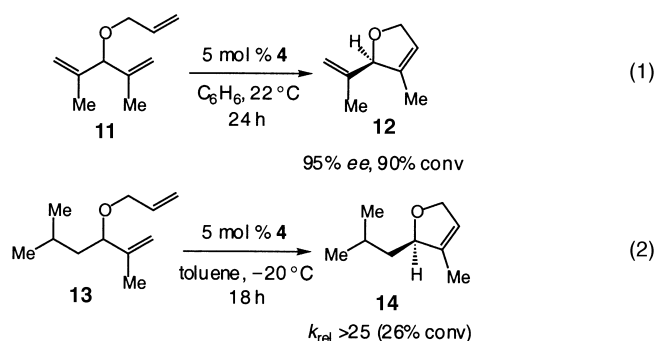
The rise of catalytic olefin metathesis as a practical and reliable method for efficient C–C bond formation has had a remarkable impact on organic and polymer synthesis.^[1] Ring-closing (RCM), ring-opening (ROM), and cross metathesis (CM) reactions have been developed in various laboratories

[*] Prof. A. H. Hoveyda, J. A. Jernelius
Department of Chemistry, Merkert Chemistry Center
Boston College, Chestnut Hill, MA 02467 (USA)
Fax: (+1) 617-552-1442
E-mail: amir.hoveyda@bc.edu
Prof. R. R. Schrock, Dr. K. C. Hultsch
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-253-7670
E-mail: rrs@mit.edu

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although **4** is less efficient than the parent homogeneous catalyst **1a** (>98% conversion to **12** in 6 h at 22 °C), excellent levels of enantioselectivity can be attained in desymmetrization (**11**→**12**) and kinetic resolution (**13**→**14**) processes.^[14] Importantly, workup simply consists of removal of the catalyst resin through filtration and evaporation of solvent in vacuo. Moreover, in contrast to unpurified products from reactions of **1a**, which are often dark brown in color, those delivered through catalysis by **4** are faint yellow which indicates lower amounts of metal impurity (see Figure 1 and related discussion below).

A variety of additional catalytic asymmetric processes can be promoted by the supported catalyst. As illustrated in

entries 1 and 2 of Table 1, asymmetric ring-opening/cross metathesis (AROM/CM) with 7-oxynorbornene substrates (for example, **15** and **17**) and styrene (2 equiv) proceed efficiently and enantioselectively.^[2d, 2h] The asymmetric conversion of cyclopentenyl ether **19** to **20** was less facile with **4** than with **1a** (57% vs >93% conv; entry 3, Table 1),^[2g] but the supported catalyst gave higher levels of asymmetric induction (33% vs 19% *ee*).^[15] Desymmetrization of **21** to afford bicyclic compound **22** (entry 4) can be promoted by supported catalyst **4** with high asymmetric induction (93% *ee*) but again less efficiently than the homogeneous variant (**1a**).^[2f] Mo-catalyzed synthesis of didehydro 1,2-silaoxepane **24** (entry 5, Table 1) is nearly as efficient with **4** as it is with **1a** (95% vs >98% conv after 2 h).^[16] Although the reaction in the presence of **4** gave the desired product less selectively, the level of asymmetric induction (81% *ee*) is synthetically useful, particularly when the relative paucity of alternative methods for the preparation of tertiary ethers and alcohols (obtained by desilylation of **24**) is considered.^[17]

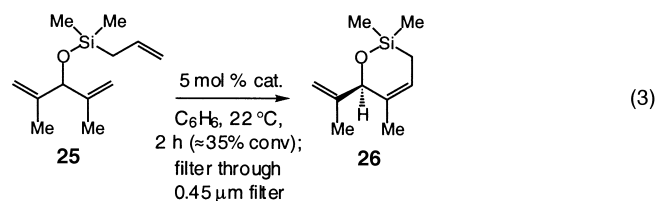
Several additional points regarding the transformations shown in Table 1 merit mention: 1) Higher substrate concentrations may be used to accelerate reactions. As an example, when Mo-catalyzed AROM of **21** (see entry 4, Table 1) was performed on a 0.5 M solution, 82% conversion was attained within 80 minutes (<2% homodimeric or oligomeric adducts formed). 2) Initial attempts to carry out catalytic asymmetric

Table 1. Catalytic asymmetric olefin metathesis reactions promoted by supported chiral catalyst.^[a]

Entry	Substrate	Product	<i>t</i> [h]	conv [%] ^[b]	Isolated catalyst yield [%] ^[c]	<i>ee</i> ^[d]	Supported catalyst conv [%] ^[b]	Supported catalyst yield [%] ^[c]	<i>ee</i> ^[d]
1 ^[e, f]			0.5	> 98	89	> 98	> 98	92	98
2 ^[e, g]			0.5	> 98	88	> 98	> 98	89	95
3			24	93	88	19	57	45	33
4			2	93	84	> 98	57	41	93
5			2	> 98	97	93	95	92	81

[a] Conditions: 5 mol % **4** (based on Mo), C₆H₆ (0.1 M), 22 °C. [b] Conversions determined by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures. [c] Yields of isolated products after silica gel chromatography. [d] Determined by chiral HPLC (Chiralcel OD for entry 1, Chiralcel AD for entry 2 and Chiralcel OJ for entry 5) and chiral GLC (Betadex column for entries 3–4). [e] Reactions performed in the presence of 2 equiv styrene. [f] Bn = benzyl. [g] MOM = methoxy methyl.

metatheses with **4** in the absence of solvent were unsuccessful. Treatment of triene **23** with **4** (5 mol % Mo) resulted in < 2 % conv after 24 h (22 °C). However, addition of C₆H₆ (~100 µL for 0.63 mmol **23**) to the mixture led to the smooth formation of **24** (> 98 % conv, 94 % yield, 71 % *ee* after 24 h). This difference in reactivity and the requirement for the presence of solvent may be attributed to the more effective access of substrate molecules to the catalytic site in the Mo-bearing resin as a consequence of polymer-swelling by the solvent. 3) As alluded to earlier, a significant advantage of the polymer-supported chiral catalyst is that simple filtration of the reaction mixture delivers materials that contain noticeably lower amounts of Mo impurity than in cases when homogeneous catalysts are utilized. For example, as illustrated in Equation (3), with **1a** as the catalyst, 91 % of the metal residue used is found as part



of the product after filtration. In contrast, when **4** is employed, only 5 % of the Mo residue contaminates the product mixture. As shown in Figure 1, this difference in purity of products directly obtained from reactions of unbound and polymer-supported catalysts is readily evident from the appearance of the respective unpurified product samples.

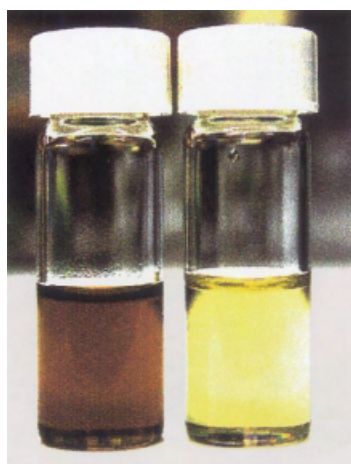
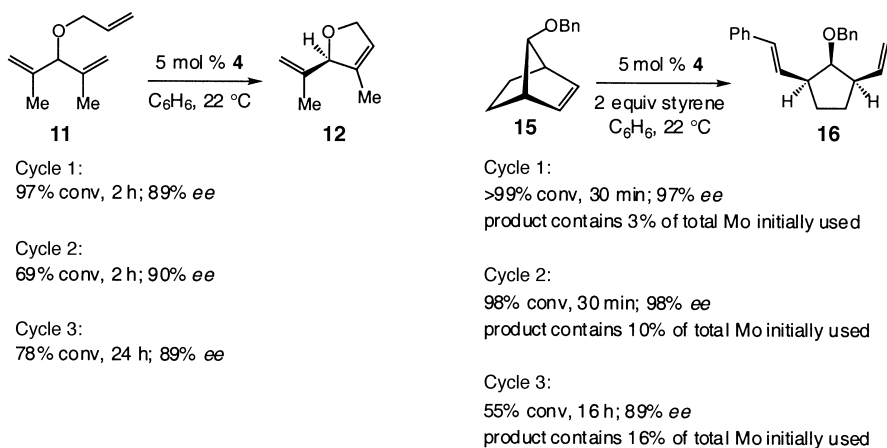


Figure 1. Difference in the appearance of solutions of asymmetric olefin metathesis product **16** obtained from reaction with **1a** (left) and supported catalyst **4** (right).

The supported chiral catalyst may be recycled. The examples shown in Scheme 3, regarding catalytic asymmetric syntheses of **12** and **16**, are illustrative. Not only does the product contain minimal Mo impurity after the first round



Scheme 3. Recycling of supported chiral metathesis catalyst **4**. Amount of Mo residue was determined by ICP-MS analysis of the unpurified product mixture.

(3 % of the total Mo used in cycle 1 for **15** → **16**), after filtration under inert atmosphere, the polymer may be utilized to effect a second round, where 98 % conversion is attained within 30 min and **16** is obtained in 98 % *ee*. Despite the observed Mo loss after the first cycle, there is little difference in reaction time and levels of enantioselectivity between the first and second cycles. In the third cycle, high enantioselectivity and conversion are still obtained but catalyst activity is notably diminished (see Scheme 3).

In brief, we have synthesized and demonstrated the utility of the first example of a polymer-supported chiral metathesis catalyst. In most cases, the polymer-bound catalyst provides similarly high levels of enantioselectivity as the corresponding homogeneous variant (**1a**); it can also be recycled with appreciable efficiency. This first generation of supported chiral Mo catalysts is, as should perhaps be expected, less active than the parent system (**1a**). The lower levels of activity exhibited by **4** may result from inefficient diffusion of substrate molecules into the polymer. The supported catalyst is expected to be less susceptible to bimolecular decomposition of highly reactive methylidene intermediates.^[18] In this regard, synthesis of more rigid polymer supports or those that represent lower Mo loading should further minimize bimolecular decomposition pathways and lead to a more robust class of catalysts. Studies towards preparation of alternative systems that give rise to more effective supported catalysts for asymmetric olefin metathesis, as well as the related applications to combinatorial synthesis of optically pure compounds, are in progress.

Experimental Section

(R)-9: A vigorously stirred suspension of **(R)-8**^[19] (412 mg, 0.586 mmol), styrene (4.20 g, 40.3 mmol), divinylbenzene (83 mg, 55 % of 0.64 mmol, remainder are ethylbenzenes), benzoyl peroxide (48 mg, 0.14 mmol, containing 30 % water), poly(vinyl alcohol) (46 mg), toluene (6 mL) and water (50 mL) was stirred at 22 °C for 1 h to homogenize the particle size. The suspension was heated to 90 °C for 24 h. The polymer was washed thoroughly with THF, methanol and pentane and dried in vacuo for 24 h to give white beads (4.4 g, 83 % yield). The resulting bis(methoxy ethoxy ether) (4.4 g) was suspended in 30 mL of a mixture of conc. HCl, methanol and THF (1:10:50) for 48 h. The polymer was isolated by filtration, washed thoroughly with THF, methanol and pentane and dried in vacuo for 24 h at

60 °C to afford the desired product (*R*)-**9** as white beads (4.3 g, 91 % yield; 76 % yield from **8**). IR (KBr): $\tilde{\nu}$ = 3510 (m), 2900–3060 (s), 2362 (m), 2344 (m), 1870 (w), 1719 (m), 1654 (w), 1602 (m), 1492 (s), 1452 (s), 1388 (w), 1270 (m), 1229 (w), 1157 (m), 1115 (w), 1028 (s), 960 (m), 823 (w), 758 (m), 699 (s) 543 (w) cm^{-1} .

(*R*)-**4**. Solid potassium hexamethyldisilazane (94 mg, 0.47 mmol) was added in portions to a suspension of (*R*)-**9** (1.00 g) in THF (10 mL). The resulting mixture was agitated for 24 h; the polymer was subsequently filtered and washed with THF (3 $\times$ 5 mL). The polymer was dried in vacuo and resuspended in THF (8 mL). At this point, solid **10** (108 mg, 0.136 mmol) was added and the mixture was agitated for 7 h. The polymer was washed with THF (4 $\times$ 5 mL) and pentane (2 $\times$ 5 mL). The resulting solid was dried in vacuo to give 1.04 g of (*R*)-**4** as a brown powder.

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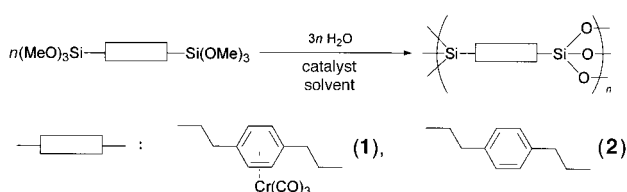
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Nonrelaxable Anisotropic Organization of Organic–Inorganic Hybrid Materials Induced by an Electric Field**

Geneviève Cerveau, Robert J. P. Corriu,* Eric Framery, Shubhajit Ghosh, and Maurizio Nobili

Hydrolytic polycondensation (sol–gel-type process)^[1] is a general route for the preparation of organic–inorganic hybrid materials.^[2–8] Nanostructured hybrid solids^[3] (class II)^[9] obtained from bis(trialkoxysilyl) precursors (MeO)₃Si–R–Si(OMe)₃ can be regarded as amorphous, since their X-ray powder diffraction diagrams exhibit no Bragg diffraction peaks. Only two or three broad diffraction bands are observed, which could be indicative of a short-range organization of the organic units, consistent with the chemical reactivity between the organic moieties in these solids.^[10, 11] In the case of precursors containing rigid, rodlike organic units, highly cross-linked materials that form a new kind of mesophase were observed in birefringence experiments.^[12, 13] Moreover, formation of this micrometer-scale organization was observed to take place after the sol–gel transition, during ageing of the solid.^[14] This permanent transition from short- to long-range organization in highly cross-linked materials is very attractive with regard to the possibilities opened up by the physical properties which can be afforded by the organic units.

Here we describe the effect of electric field as a controlling factor for the self-organization of organic groups attached to a hybrid material. The hydrolytic polycondensation of precursor **1**,^[15] which has a dipole moment and is silylated in the α and ω positions to prevent relaxation of the solid formed, was performed in an electric field. The dipole moment was calculated by ZINDO/1 simulation with the program Hyperchem to be 2.37 D. The dipole moment is introduced by a Cr(CO)₃ group, and for comparison experiments were performed with **2**, which lacks the Cr(CO)₃ group (Scheme 1). Birefringence was selected for testing for the presence of



Scheme 1. Polycondensation of bis(trialkoxysilyl) precursors **1** and **2**.

[*] Prof. R. J. P. Corriu, G. Cerveau, E. Framery, S. Ghosh
Laboratoire de Chimie Moléculaire et Organisation du solide
UMR 5637, Université Montpellier II, cc 007
Place E. Bataillon, 34095 Montpellier Cedex 5 (France)
Fax: (+33)4-67-14-38-52
E-mail: cmos@crit.univ-montp2.fr
M. Nobili
Groupe de Dynamique des Phases Condensées, UMR 5581
Université Montpellier II
Place E. Bataillon, 34095 Montpellier Cedex 5 (France)

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organization, since it evidences an anisotropic order on the micrometer scale corresponding to the wavelength range used for its measurement (visible light). We therefore studied the formation of solids in glass cells coated with transparent indium tin oxide (ITO), which allow the visualization of optical properties under a polarizing microscope. Since a strong electric field (1 V μm^{-1}) is necessary, we selected experimental conditions that avoid electrolysis of reagents. Hence, we replaced the nucleophilic (NBu₄F or NH₄F) or acid catalyst (HCl) by the neutral nucleophile *N*-methylimidazole (NMI), the catalytic efficacy of which was recently demonstrated.^[16] To minimize the amount of water present in the cell we used water vapor as reagent.

The following procedure was used: a homogeneous mixture of precursor, THF, and NMI was introduced by means of capillarity into the cell, which was placed in a closed glass apparatus providing an atmosphere with 60% humidity (vacuum/NaBr solution). Thus, the gel formed by slow diffusion of gaseous water. In all cases, the cells were inspected at different stages of the hydrolysis process by optical microscopy with polarized light. The observations were made in the direction of the field. In the case of precursor **1**, the initial **1**–THF–NMI mixture was dark when analyzed by polarizing optical microscopy; this observation is characteristic of an isotropic medium. Interestingly, when a dc electric field was applied (1 V μm^{-1}) normal to the glass plates, hydrodynamic movement was observed in the entire cell. Gelation occurred after 22–24 h. The electric field was switched off at this stage. Analysis of the cell by polarizing optical microscopy revealed the presence of bright regions corresponding to a birefringent medium (1.70 $\times 10^{-3}$). The optical axis and the birefringence were not homogeneous throughout the cell (Figure 1). However, it was possible to



Figure 1. Birefringent gel obtained from **1** in an electric field.

observe complete light extinction at each point in the cell when the sample was rotated through 45°. We checked that the integrity of the organic unit was preserved under the electric field by using a thicker cell (100 μm), which allowed enough material to be collected for IR analysis. This cell was subjected to a field of 0.2 V μm^{-1} and then opened. The product exhibited the same IR spectrum as that previously reported.^[15] We also studied the evolution of birefringence with time and observed great stability, since no change was observable after two years. A similar experiment performed

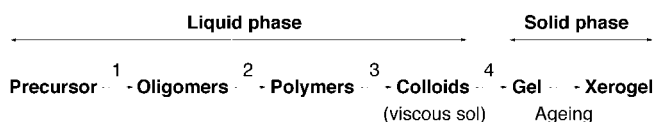
without an electric field led after 5 d to a gel which did not exhibit any birefringence.

The precursor **2**, which has no dipole moment, was treated under the same conditions: initial precursor–THF–NMI mixture, electric field of about $1 \text{ V } \mu\text{m}^{-1}$. A hydrodynamic movement was observed for a fraction of a second, and a gel formed after 32 h, instead of 72 h without an electric field. However, in both cases, no birefringence was observed. Moreover, as **1**, too, does not exhibit any birefringence when the polycondensation at silicon is performed in a cell without an electric field, we can conclude that the micrometer-scale organization we have observed in the case of **1** is induced by the electric field, which imposes the orientation of the dipole moments.

Besides the observation of birefringence, the effect of the electric field on the gelation time is noteworthy. For both organic precursors **1** and **2** a shorter gelation time is always observed in an electric field. This might be due to the hydrodynamic movements that it induces.

This observation prompted us to perform experiments with plates that were half-coated by transparent ITO. This made it possible to observe **1** in the same cell with (ITO coating) and without an electric field (no coating). In the ITO-coated part we observed the formation of birefringent gel after 22–24 h. In the other part of the cell neither birefringence nor formation of a solid was observed. Surprisingly, however, 2 d after switching off the electric field a birefringent gel also appeared in this part of the cell. Moreover, this birefringence had the same characteristics as that observed in the part under the electric field, and rotation of the sample under the polarizing microscope led to the same observations in the two parts of the cell in terms of organization or birefringence. This observation was completely unexpected: although, in the absence of electric field the solid derived from **1** did not exhibit any birefringence. The micrometer-scale organization in the second experiment occurred in that part of the cell that was not subjected to the controlling factor of organization. Furthermore, this organization was observed 2 d after the electric field had been switched off. Experiments were performed in which the intensity of the field was varied from 0.2 to $1 \text{ V } \mu\text{m}^{-1}$. In all cases, a gel formed in the ITO-coated part of the cell after 20–24 h, whereas gelation occurred in the other part 2 d after the electric field had been switched off. At 0.2 and $0.4 \text{ V } \mu\text{m}^{-1}$, no birefringence was observed in any part of the cell. In contrast, at 0.6 and $1 \text{ V } \mu\text{m}^{-1}$, the phenomenon described above was evident under polarized light. These results confirm the crucial importance of the electric field as a controlling factor that induces organization not only in the first part but also in the second, which was not subjected to the electric field.

We propose an explanation that takes into account the hydrodynamic movement induced by the electric field. Let us consider the general equation of sol–gel transition (Scheme 2). During steps 1–3, exchange of matter is occurring between the two parts of the cell, since the material is a liquid. At this moment the two parts have the same composition. This means that the polycondensation at silicon, which transforms the molecular precursor into a cross-linked material, is more or less at the same level in the two parts of



Scheme 2. General scheme of the sol–gel process.

the cell. The organization induced by the electric field is permanently exchanged with the second part of the cell. In other words, the degree of organization induced by polymers in which the dipole moments of the cross-linked organic units are oriented is the same in the two parts of the cell during polycondensation in the liquid phase. However this exchange becomes slower when the viscosity increases with the formation of colloids in the viscous sol. Under these conditions the part of the cell that is subjected to the electric field becomes more organized. Thus, the sol–gel transition and the ageing step permit the formation of birefringence at first in the part submitted to the field and after some time in the other part of the cell.

To explain the presence of birefringence in the second part we considered earlier results which indicated that both texture (specific surface area, porosity, etc.) and self-organization of the organic units in the solid are controlled not only by polycondensation in solution (steps 1–3), but also during ageing in the solid state.^[17] Thus, formation of this new type of birefringent, highly cross-linked material starts during the ageing step when the solid is already formed, since the highly cross-linked solid formed just after the sol–gel transition does not exhibit any birefringence.

In the liquid phase the two parts of the cell contain the same amount of colloids in which the organic units have been orientated by the electric field. After the sol–gel transition these colloids are linked to each other, and the reorganization of Si–O–Si bonds that occurs at the surface of colloids in the parts of the cell with and without electric field lead to the same birefringent material. These experiments show that the formation of self-organized domains in solution is a sufficient condition for inducing micrometer-scale organization during ageing. The electric field does not make any significant difference during this step of long-range ordering of domains with short-range order.

In conclusion, we previously observed self-organization due to van der Waals-type interactions between the organic units^[12] during the polycondensation at silicon. In the case of rigid, rodlike organic groups, short-range order was indicated by X-ray diffraction peaks that were related to the length of the organic spacer. The short-range order was also confirmed in experiments performed with dilution by $\text{Si}(\text{OMe})_4$ in the solid.^[18] In the present study, the short-range order is induced by the electric field, which imposes vectorial orientation on the $\text{Cr}(\text{CO})_3$ groups in the same direction and leads to a microscale order. Moreover, the experiments presented here showed that the existence of self-organized domains in solution is a sufficient condition for the formation of this microscale ordering in the solid phase during ageing. Finally, the stability of birefringence over the time (two years without change) demonstrates that the dipole moments do not relax after switching off the electric field, and this suggests the

possibility of nonlinear optical properties.^[19, 20] This behavior is certainly due to the high degree of cross-linking and to the appropriate α, ω arrangement of the silicon-containing groups in the precursor, which prevents any relaxation.

Experimental Section

Preparation of the cells: The ITO-coated and normal glass plates (20×20 mm) were cleaned with ethanol, acetone, sulfochromic acid, and finally water. Two plates were then mounted on each other and attached with UV-sensitive glue at four corners. The parallelism of the glass plates and the cell thickness were checked by measuring the interference fringes. The cell was then placed under a UV lamp for 10 min. Thickness was measured by UV/Vis spectroscopy and was (10 ± 2) μm . The wires on each cell were soldered with indium pellets (15 mm, 99.99% pure).

Preparation of the gels: A solution of NMI (35 mol %, 0.205 mmol) in THF (277 μL) was added to a solution of the precursor (0.587 mmol) in THF. The homogenous solution was introduced into the cell, which was filled by capillarity. The cell was then placed inside a glass apparatus with a chamber for saturated NaBr solution, and vacuum was then applied to give an atmosphere with 60% humidity. Finally, a potential difference of 10 V, which corresponds to a dc electric field of about $1 \text{ V } \mu\text{m}^{-1}$, was applied across the two plates of the cell. The evolution was constantly monitored under the microscope during condensation. The optical properties of the material were observed through a Laborlux 12 POLS polarizing microscope. Photographs were taken with a Leica MPS28 camera.

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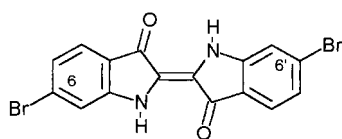
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Akashins A, B, and C: Novel Chlorinated Indigoglycosides from *Streptomyces* sp. GW 48/1497**

Rajendra P. Maskey, Iris Grün-Wollny,
Herbert H. Fiebig und Hartmut Laatsch*

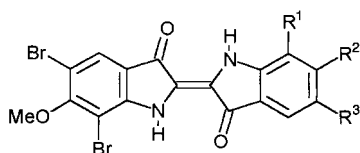
Dedicated to Professor Wolfgang Lüttke

Indigo and its dibromo derivative, purple **1a** are amongst the most important dyes. They were already used in a ancient civilizations^[1] and indigo is still an industrially important dye. Numerous derivatives have been synthesized, not only for dyeing textiles, but also for important theoretical investigations of the chromophoric properties of indigo. The pigment



1a

1b: 5,5'-Cl instead of 6,6'-Br



2a: $R^1, R^3 = H, R^2 = Br$

2b: $R^1, R^3 = Br, R^2 = OMe$

can be obtained from various higher plants such as *Baphicanthus cusia* (Acanthaceae), *Calanthe veratrifolia* (Orchidaceae), *Isatis tinctoria* (Brassicaceae), and *Polygonum tinctorium* (Polygonaceae), by a process that involves its formation from precursors such as indican and isatan. Indigo has also been isolated from fungi (*Schizophyllum commune*,^[2] *Agaricus campester*^[3]) and has even been detected in the urine, blood plasma, and haemofiltrate of patients^[4] suffering from metabolic disorders (Blue-Diaper syndrome). Whereas numerous derivatives of naturally occurring chromophores are also found in nature, only three derivatives of the blue indigo

isomer (indigotin) occur: in addition to the well-known Tyrian purple (6,6'-dibromoindigo, **1a**)^[5] from the purple snail, only derivatives **2a** and **2b** from the marine invertebrate *Ptychodera flava laysanica* are known.^[6]

We have now isolated derivatives of 5,5'-dichloroindigo (**1b**) from the terrestrial *Streptomyces* sp. GW 48/1497. The chromophore **1b** was previously unknown as a natural product. The derivatives are unsymmetrically monoglycosylated at the N1 atom of **1b**. Even synthetic N-glycosides of indigo have not been described previously. In addition to daidzein and genistein 7-methyl ether, which presumably originate from the nutrient medium, we also isolated 2-(3-indolyl)ethanol.

The (+)- and (–)-ESI mass spectra of the compounds, termed akashins A, B, and C,^[7] showed molecular weights of 475, 517, and 545 Dalton. The isotope pattern of the molecular ion indicated the presence of two chlorine atoms. The typical UV spectra, the chemical shifts of the sp^2 carbon atoms, the coupling constants of the arene protons in the ^1H NMR spectrum, as well as the H,H-COSY, HMQC, and HMBC correlations corroborated the structure of the aglycon (Figure 1). Furthermore, this structure is consistent with the fragment ion at m/z 330, which is common to all three

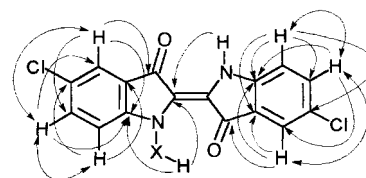


Figure 1. H,H-COSY ($\leftrightarrow$) and HMBC couplings ($H \rightarrow C$) of the aglycon of the akashins; X = sugar residue.

pigments, and with the formula $C_{16}H_8N_2O_2Cl_2$, which was determined by means of high-resolution mass spectrometry. The akashins are derivatives of 5,5'-dichloroindigo **1b** in which the nitrogen atom of one half of the chromophore is N-glycosidically bound to a sugar residue, as shown by long-range coupling experiments. Surprisingly, the resulting UV/Vis absorption shows only a minor hypsochromic shift relative to that of 5,5'-dichloroindigo,^[8] which was not expected based on studies of *N,N'*-dimethylindigo.^[9]

A comparison of the coupling constants of the akashins (between $^3J = 8.6$ and 15.8 Hz) with those of bagougeramines A and B^[10] ($^3J_{ax,ax} = 9.3$ – 10.7 Hz), spicamycin tetraacetate^[11] ($^3J_{ax,ax} = 10.5$ Hz), and methyl 2,3-di-*O*-acetyl-4,6-dideoxy-4-(*N,N'*-dimethylamino)- α -D-mannopyranoside^[12] ($^3J_{ax,ax} = 8.2$ Hz) reveals that all the ring protons of the sugar residue of **3a**–**3c** adopt axial positions. This is confirmed by the small axial/equatorial and equatorial/equatorial coupling constants, for example, in spicamycin tetraacetate^[11] ($^3J = 3.0$ and 3.5 Hz) and methyl 4-bromo-4,6-dideoxy- α -D-talopyranoside^[13] ($^3J = 1.5$ – 4.1 Hz). To confirm further the configuration of the sugar residue, the absolute energy minimum of **3a** was calculated by using the HUNTER program.^[14] The coupling constants determined for the calculated conformation by using PCModel agreed well with the experimental values.

[*] Prof. Dr. H. Laatsch, Dr. R. P. Maskey
Institut für Organische Chemie
Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-399660
E-mail: HLAATSC@gwdg.de

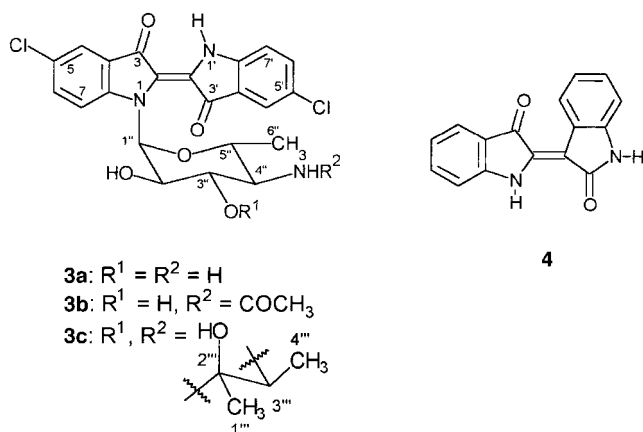
Dr. I. Grün-Wollny
Fa. bioLeads, Heidelberg (Germany)
Prof. Dr. H. H. Fiebig
Oncotest GmbH, Freiburg (Germany)

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The sugar residue is 4-acetamido-4,6-dideoxyglucopyranose; the corresponding amino sugar is a component of more than 120 natural products, for example, tallysomyacin,^[15] amicetin,^[16] calicheamicin,^[17] and norplicaceticin,^[18] and is found in both the D and L configurations. It has thus far not been possible to determine which form occurs in the akashins, as a result of the small quantities of material obtained. Further investigations are required to determine if the extremely large optical rotation of the akashins is a result of a helical conformation of the chromophore.

Similar to indigo, 5,5'-dichloroindigo **1b** is poorly soluble in cold common organic solvents. The akashins are even less soluble than **1b** in nonpolar solvents; however, they are more soluble in methanol and dimethyl sulfoxide, but not in water.

Although indigo itself shows no biological activity, the akashins **3a–c** are active against various human tumor cell



lines (CNCL SF268, LCL H460, MACL; colon carcinoma CCL HT29, melanoma MEXF 514L, lung carcinoma LXFA 526L, LXFL, and 529L, breast cancer MCF-7, kidney tumors PRCL PC3M and RXF 631L) with IC₅₀ values of about 2.8 µg mL⁻¹ and IC₇₀ values of > 3 µg mL⁻¹. Thus they resemble the 2,3-coupled indirubin (**4**), an ingredient of the Chinese drug Danggui Longhui Wan, for which strong antitumor activity was found.^[19] In contrast to indigo, however, the akashins are not accompanied by red isomers.

Experimental Section

The terrestrial *Streptomyces* GW 48/1497 (bioLeads, Heidelberg) was fermented and handled under standard conditions^[20] on a soya-mannitol medium (shaker culture, 15 L divided into 75 1-L baffled flasks), 3 days, 28 °C, 110 Upm).

After separation on silica gel, the blue pigment fraction was purified by means of preparative thin-layer chromatography (PTLC) (CHCl₃/15% MeOH/0.1% AcOH). Concentration of the eluate from band at R_f = 0.15 (R_f = 0.11, CH₂Cl₂/10% MeOH) gave **3a** (35.6 mg) as a blue substance which is only sparingly soluble in methanol. Further purification of two subsequent fractions led to the isolation of **3b** and **3c** as dark blue substances: purification on Sephadex LH-20 (3 × 70 cm, CHCl₃/MeOH (40%)) gave **3b** (6 mg; R_f = 0.48, CHCl₃/17% MeOH/0.2% AcOH; R_f = 0.22, CH₂Cl₂/10% MeOH); purification of the second fraction on Sephadex LH-20 and PTLC (20 × 20 cm, CHCl₃/10% MeOH) gave **3c** (5 mg; R_f = 0.49 (CHCl₃/17% MeOH/0.2% AcOH; R_f = 0.52 (CH₂Cl₂/10% MeOH).

Akashin A (**3a**): ¹H NMR ([D₆]DMSO, 300 MHz): δ = 11.01 (br s, H/D exchangeable, 1H; N'-H), 7.75 (d, ³J = 1.8 Hz, 1H; 4-H), 7.65 (dd, ³J = 8.8 Hz, ⁴J = 2.2 Hz, 1H; 6-H), 7.59, 7.57 (m, 3H; 4'-, 7-, 6'-H), 7.44 (dd, ³J = 8.5 Hz, ⁵J = 0.6 Hz, 1H; 7'-H), 5.80 (d, ³J = 9.2 Hz, 1H; 1'-H), 5.64 (br s, H/D exchangeable, 1H; OH), 5.11 (d, H/D exchangeable, ³J = 7.2 Hz, 1H; OH), 3.79 (qd, ³J = 9.5 Hz, ³J = 6.1 Hz, 1H; 5''-H), 3.62 (dd, ³J = 15.8 Hz, ³J = 8.6 Hz, 1H; 2''-H), 3.30 (dd, ³J = 15.8 Hz, ³J = 9.8 Hz, 1H; 3''-H), 2.81 (t, ³J = 9.8 Hz, 1H; 4''-H), 1.43 (d, ³J = 6.0 Hz, 3H; 6''-H₃); ¹³C NMR ([D₆]DMSO, 125.7 MHz): δ = 186.4 (CO-3), 185.3 (CO-3'), 150.6 (C-7a'), 148.7 (C-7a), 135.6 (CH-6'), 134.5 (CH-6), 126.4 (C-5), 124.7 (C-5'), 124.3 (C-2), 123.9 (C-2'), 123.8 (C-3a), 123.0 (CH-4'), 122.5 (CH-4), 120.0 (C-3a') 117.7 (CH-7), 115.0 (CH-7'), 87.6 (CH-1'), 74 (CH-3'), 72.1 (CH-5''), 69.7 (CH-2''), 57.3 (CH-4''), 18.0 (5''-Me); (+)-ESI-MS: m/z (%): 976 (47) [2M+Na], 974 (87) [2M+Na], 972 (65) [2M+Na], 502 (10) [M+], 500 (60) [M+], 498 (98) [M+], 480 (8) [M+1], 478 (32) [M+1], 476 (48) [M+1], 335 (11) [M - sugar], 333 (65) [M - sugar], 331 (100) [M - sugar], 146 (84) [sugar]; (-)-ESI-MS: m/z (%): 478 (33) [M - 1], 476 (100) [M - 1], 474 (98) [M - 1]; UV/Vis (MeOH): λ_{max} (lge) = 241 (4.33), 290 (4.23), 619 (4.01) nm; IR (KBr): ν̄ = 3426, 2927, 1636 (CO), 1610, 1463, 1386, 1306, 1259, 1180, 1120, 1084, 1048, 883, 829, 764, 710, 649, 623, 585 cm⁻¹; [α]_D²⁵ = +2560° (c = 12.5 µg mL⁻¹, MeOH); calcd for C₁₆H₈N₂O₂Cl₂ (M - sugar + H): 329.9962, found: 329.9962.

Akashin B (**3b**): ¹H NMR ([D₆]DMSO, 500 MHz): acetate signal at δ = 1.86 (s, 3H; NHAc), other signals similar to those of **3a**; ¹³C NMR ([D₆]DMSO, 125.7 MHz): δ = 170.0 (NHCO-Me), 23.1 (NHCO-Me), other signals similar to those of **3a**; UV/Vis (MeOH): λ_{max} (lge) = 244 (4.34), 291 (4.28), 618 (4.03) nm; IR (KBr): ν̄ = 3430, 2929, 1641 (CO), 1610, 1558, 1464, 1384, 1305, 1259, 1182, 1087, 1053, 884, 824, 764, 709 cm⁻¹; [α]_D²⁵ = +2840° (c = 14 µg mL⁻¹, MeOH).

Akashin C (**3c**): ¹H NMR (CD₃OD, 500 MHz): δ = 7.74 (d, ³J = 9.1 Hz, H/D exchangeable, 1H; N-H), 7.70 (d, ⁴J = 2.1 Hz, 1H; 4-H), 7.58 (m, 3H; 6-H, 7-H, 4'-H), 7.49 (dd, ³J = 8.8 Hz, 1H; 6'-H), 7.18 (d, ³J = 8.7 Hz, 1H; 7'-H), 6.12 (d, ³J = 9.2 Hz, 1H; 1''-H), 3.97 (t, ³J = 10.1 Hz, 1H; 2''-H), 3.95 (dq, ³J = 9.6 Hz, ³J = 6.6 Hz, 1H; 5''-H), 3.92 (t, ³J = 9.6 Hz, 1H; 3''-H), 2.82 (q, ³J = 6.5 Hz, 1H; 3''-H), 2.70 (t, ³J = 9.6 Hz, 1H; 4''-H), 1.45 (d, ³J = 6.6 Hz, 3H; 6''-H₃), 1.20 (d, ³J = 6.5 Hz, 3H; 4''-H₃), 1.18 (s, 3H; 1''-H₃); ([D₆]DMSO): additionally δ = 10.98 (s, H/D exchangeable, 1H; N'-H); ¹³C NMR (CD₃OD, 125.7 MHz): δ = 188.8 (CO-3), 187.4 (CO-3'), 152.0 (C-7a'), 150.5 (C-7a), 137.1 (CH-6'), 136.0 (CH-6), 129.9 (C-5), 129.0 (C-3a), 127.3 (C-5'), 126.6 (C-2'), 125.6 (C-2), 124.6 (CH-4'), 124.1 (CH-4), 122.0 (C-3a'), 118.7 (CH-7), 115.2 (CH-7'), 96.7 (C-2'''), 89.7 (CH-1''), 75.1 (CH-5''), 75.0 (CH-3''), 69.2 (CH-2''), 62.9 (CH-4''), 59.2 (CH-3''), 25.6 (1''-Me), 18.0 (5''-Me), 16.3 (3''-Me); (+)-ESI-MS: m/z (%): 570 (4) [M+Na], 568 (16) [M+Na], 546 (28) [M+1]; (-)-ESI-MS: m/z (%): 548 (54) [M - 1], 546 (96) [M - 1], 544 (100) [M - 1]; UV/Vis (MeOH): λ_{max} (lge) = 241 (4.58), 290 (4.43), 619 (4.20) nm; IR (KBr): ν̄ = 3447, 1638 (C=O), 1610, 1467, 1390, 1308, 1260, 1180, 1080, 1049, 887, 829, 764, 710 cm⁻¹; [α]_D²⁵ = +3100° (c = 5.8 µg mL⁻¹, MeOH).

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Wet Chemistry Synthesis of β -Nickel Aluminide NiAl**

Helmut Bönemann,* Werner Brijoux, Hans-Werner Hofstadt, Teyeb Ould-Ely, Wolfgang Schmidt, Bernd Waßmuth, and Claudia Weidenthaler

Owing to its extraordinary physical properties β -nickel aluminide NiAl is an important raw material,^[1] which on the one hand has a lower density than nickel,^[2] while on the other at 1638 °C^[3] exhibits a significantly higher melting point than nickel (1453 °C) and aluminum (660 °C). Since a dense aluminum oxide layer is formed, even at low surface oxidation, NiAl has high thermal stability and resistance to atmospheric oxygen.^[4] Owing to its high resistance towards environmental influences NiAl can be used as a Ni replacement, for example in gas turbine blades and automobile construction.^[5]

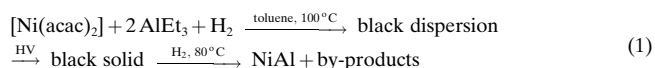
The mechanical properties of NiAl are highly dependent upon the conditions of preparation and grain size.^[6] Traditionally,

the coarse-grained material ($\varnothing > 1 \mu\text{m}$), which is produced by milling^[7] at 800–900 °C (“mechanical alloying”) is brittle at room temperature. Refining the particle diameter into the nanometer range increases ductility, strength, and hardness.^[8] Thus nanocrystalline NiAl, which was produced by gas-phase condensation,^[9] exhibits a considerably greater microhardness than the milled material. Mechanical alloying is associated with two significant disadvantages: 1) the particles readily agglomerate to larger units at the relatively high milling temperature, and 2) large amounts of Ni and Al remain together unalloyed.

Buhro et al.^[10] have described a method for the wet chemical synthesis of NiAl by the reaction of suspended NiCl_2 with LiAlH_4 in mesitylene while refluxing under an inert atmosphere. NiAl is not formed directly during the reaction but only by subsequently heating the solid to about 550 °C. The by-products LiCl and AlCl_3 must be removed from the solid by sublimation at 700–750 °C, whereby a relatively coarse-grained material is obtained. Withers et al.^[11] reacted NiCl_2 with Al powder at 750 °C and after purification of the crude product from AlCl_3 by sublimation, obtained a Ni_3Al powder with a grain size in the micrometer range ($\varnothing = 1.4\text{--}1.8 \mu\text{m}$). Abe and Tsuge^[12] obtained a mixture of NiAl and Ni_3Al powder by the reaction of NiCl_2 and AlCl_3 with ammonium carboxylates and subsequent heating of the resulting Ni and Al carboxylates up to 1400 °C under argon.

As early as 1955 Ziegler and co-workers described the formation of colloidal nickel in the reaction of $[\text{Ni}(\text{acac})_2]$ ($\text{acac} = \text{acetylacetonate}$) with AlR_3 ($\text{R} = \text{alkyl}$) in solution.^[13] This finding was used later by Wilke et al. to explain the „nickel effect“ in the polymerization reaction of ethene on AlR_3 ,^[14] in this context the reactions of organonickel complexes such as $[\text{Ni}(\text{bpy})\text{Me}_2]$ ($\text{bpy} = 2,2\text{--}bipyridine$), $[\text{Ni}(\text{cdt})]$ ($\text{cdt} = \text{cyclododeca-1,5,9-triene}$), and $[\text{NiCl}_2(\text{PR}_3)_2]$ with AlR_3 or AlHR_2 were also investigated. Wilke et al. concluded that in these reactions thermolabile addition compounds of nickel core complexes were formed with AlR_3 or AlHR_2 .^[14]

Repeating the Ziegler experiments in an autoclave under H_2 we obtained a black dispersion, which according to transmission electron microscopy (TEM) contained colloidal nickel [Eq. (1)]. The reaction of $[\text{Ni}(\text{acac})_2]$ with $\text{Al}i\text{Bu}_3$ gave particles with a mean diameter of $\varnothing = 2.8 \text{ nm}$. After removal of the solvent and excess AlEt_3 in high vacuum (HV) a hard black solid remained. By hydrogenation at 80 °C under pressure (5 MPa) we obtained from this a black powder, which according to elemental analysis contained NiAl and larger amounts of an undefined, inseparable by-product [Eq. (1)].

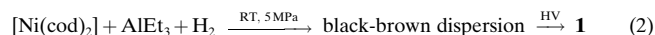


The reaction of $[\text{Ni}(\text{cod})_2]$ ($\text{cod} = \text{cycloocta-1,5-diene}$) with AlEt_3 at room temperature in a molar ratio of 1:1 in toluene under a H_2 pressure of 5–10 MPa gave a clear black-brown dispersion from which a black solid precipitates. After

[*] Prof. Dr. H. Bönemann, Dr. W. Brijoux, H.-W. Hofstadt, Dr. T. Ould-Ely, Dr. W. Schmidt, B. Waßmuth, Dr. C. Weidenthaler Max-Planck-Institut für Kohlenforschung Abteilung Heterogene Katalyse Postfach 101353, 45466 Mülheim an der Ruhr (Germany) Fax: (+49)208-306-2983 E-mail: boennemann@mpi-muelheim.mpg.de

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removal of the solvent by distillation and drying under high vacuum a solid, highly air-sensitive intermediate **1** is isolated, which according to elemental analysis contains Ni and Al as well as larger amounts of hydrocarbons [Eq. (2)].



As a qualitative GC analysis of the distilled solvent showed, complexed cod is hydrogenated to cyclooctane during the reaction; the ethyl ligand in AlEt_3 is converted into butane and butylcyclooctane. Ethene, ethane, butene, and hydrogen were detected in the gas phase by mass spectrometry.

Compound **1** was investigated in more detail by IR spectroscopy as well as by differential scanning calorimetry (DSC) and thermogravimetry (TG) coupled with mass spectrometry (MS). A ^1H NMR spectrum could not be recorded because of the insolubility of **1** in apolar solvents. The IR spectrum (Figure 1) clearly shows the vibrational bands of aliphatic C–H bonds in the region just below 3000 cm^{-1} as well as the deformation bands of the Al alkyl groups and the bands of the Al–C bond in the fingerprint region. In addition a band at 1591 cm^{-1} appears, which presumably originates from an Al–H vibration.

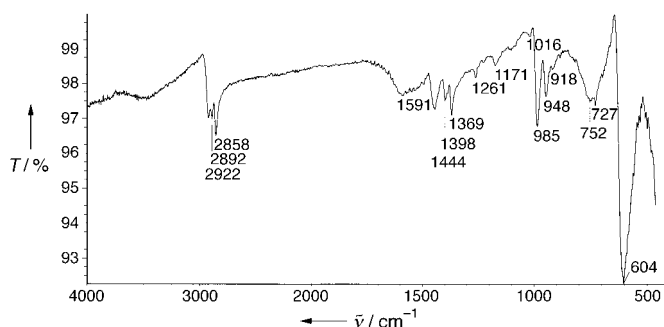


Figure 1. IR spectrum of **1**.

According to DSC/TG/MS analysis of **1** (Figure 2a, b) above a temperature of 70°C a loss in weight occurs with release of hydrogen (m/z 2) and cyclooctane (m/z 112, 111). Signals for the C_1 to C_8 fragments are also found in this region. The cod ligand could not be detected in the sample. From above about 140°C the formation of ethene and, in smaller amounts, ethane (m/z 28 and 30, respectively) occurs. Above about 200°C methane is formed by hydrogenation of ethene (m/z 16, 15). Small amounts of oxygen, which occur as an impurity in the argon, react (reduction of the intensity of the signal for m/z 32) with hydrogen to form water (m/z 18); the hydrocarbons too are also oxidized to a slight extent. Up to a temperature of 400°C the sample loses overall 7.5 wt %. A further loss in weight is observed only above temperatures of 900°C . This loss in mass is associated with the release of lower hydrocarbons such as methane, ethene, propane, and can be attributed to the decomposition of carbon-rich hydrocarbons (coke). According to dynamic DSC/TG/MS this process is clearly still not complete at 1500°C . The loss up to this temperature is a further 7.2 wt.% of the total mass. Thus on

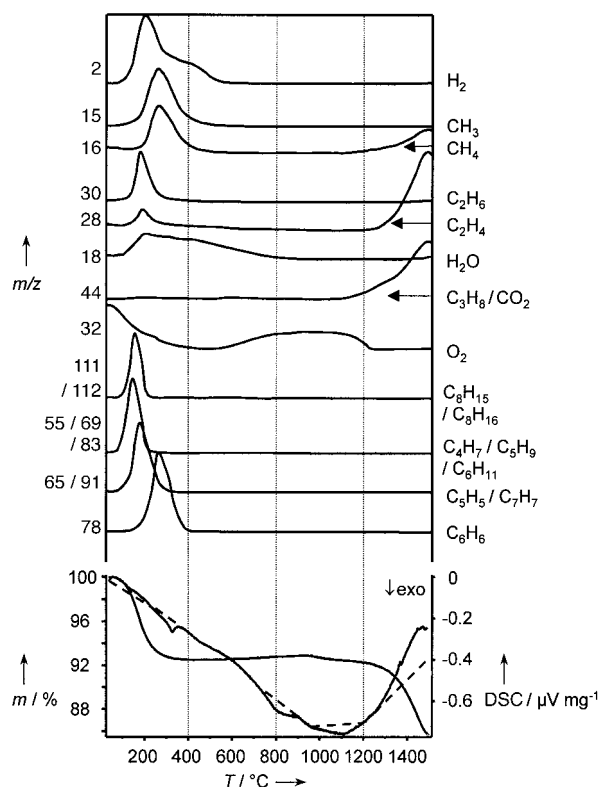


Figure 2. Top: MS curves, recorded during the TG/DSC measurement; the curves are not to scale to allow clearer presentation of lower intensities. Bottom: TG/DSC curves of **1**, measured with a heating rate of $10^\circ\text{C min}^{-1}$ under argon.

heating the sample up to temperatures of 400°C under argon first hydrogen, ethene, ethane, cyclooctane, methane, and coke, which in turn partially fragments to lower hydrocarbons above 900°C , are formed.

The following reaction course can be proposed from the DSC/TG/MS experiments together with the IR measurements, GC analysis, and from comparison with literature data: cod is cleaved from $[\text{Ni}(\text{cod})_2]$ which is hydrogenated to cyclooctane. AlEt_3 decomposes into $(\text{AlEt}_2\text{H})_2$ and ethene, which further reacts partially to butane. To a small extent, however, cod adds to AlEt_3 or to AlH . The AlH species coordinates through a hydrogen bond to atomically dispersed nickel in the toluene and stabilizes this in colloidal form with formation of the black-brown toluene dispersion. [Eq. (1)]. That such a bridging bond formation is possible comes from the results of Wilke et al.^[14] A Ni–H–Al bridge in $[(\text{cdt})\text{Ni–H–AlEt}_2]$ was established directly by low-temperature ^1H NMR measurements. The broad Al–H band in the IR spectrum of the solid **1** also suggests a Ni–H–Al bridge (Figure 1). The crystal structure of $[(\text{cdt})\text{Ni–H–AlMe}_2(\text{C}_7\text{H}_{13}\text{N})]$ serves as a model for stabilization with hydrogen bonds.^[15] In this complex Ni and Al are each tetrahedrally coordinated and are connected by an angular hydrogen bond. Because of the Al–H–Ni angle of 116° the Ni–Al distance is only about 273 pm, which is indicative of a metal–metal interaction. In agreement with the analysis and the comparative data from the literature **1** may be described as a matrix of nickel atoms coordinatively surrounded by AlEt_2H (Figure 3).

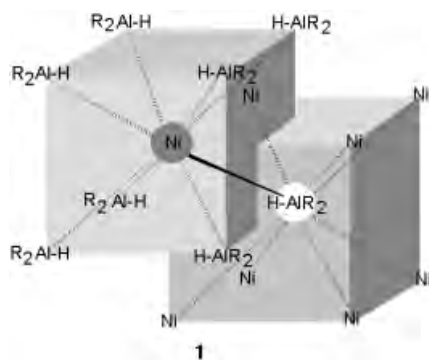


Figure 3. Presumed structure of the amorphous intermediate **1**.

To prepare the NiAl powder **2** compound **1** is first treated with H_2 at about $200^\circ C$ without pressure (or at a pressure of about 5 MPa). In this way the ethyl groups bonded to the Al centers are hydrogenated. Annealing at about $300^\circ C$ under an inert atmosphere finally gave with gas evolution (H_2 and C_2 hydrocarbons) almost hydrocarbon-free, high purity **2**.^[16]

Compound **2** was characterized by X-ray diffraction (XRD) and scanning electron microscopy (SEM): NiAl (β -nickel aluminide; Ni content 46.6–57.7 atom %) crystallizes with a CsCl structure. The space group is $Pm\bar{3}m$, the lattice parameter a ($=b=c$) is, according to the Ni fraction, 287.04 ($Ni_{46.6}Al_{53.4}$ and $Ni_{57.7}Al_{42.3}$, respectively) to 288.72 ppm ($Ni_{50}Al_{50}$).^[17] In the diffractogram (Debye–Scherrer image, $Cu_{K\alpha 1}$ radiation, $\lambda = 1.540598 \text{ \AA}$) of **2**, reflections at $2\theta = 30.9^\circ$, 44.4° , 54.0° , 64.7° , 71.0° , and 81.9° are observed, which supports the presence of NiAl (Figure 4).

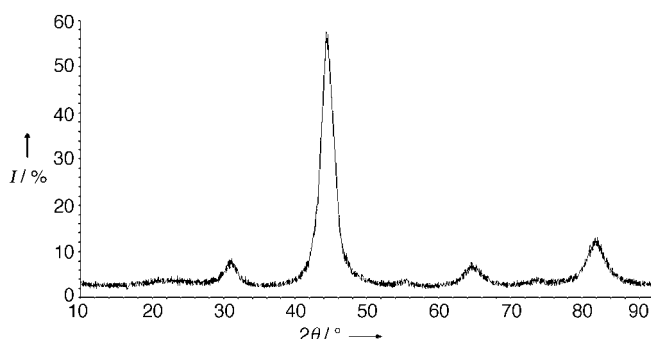


Figure 4. Powder diagram of **2** after hydrogenation and annealing at $300^\circ C$.

To test this **2** was annealed to $1000^\circ C$ under an inert atmosphere leading to the formation of NiAl powder **3**. This gave intense, sharp reflections which can be assigned unambiguously to NiAl. In addition weak reflections of the intermetallic Ni_3Al phase (α -nickel aluminide) formed to a small extent can also be observed (Figure 5a).

The measured and calculated intensities are compared in Table 1. The calculated intensities were obtained from a crystal structure refinement according to the Rietveld method.^[18] The CsCl structure was used as starting model for the refinement in which the 1a position (0,0,0) was initially completely occupied with Ni, the 1b position ($\frac{1}{2}, \frac{1}{2}, \frac{1}{2}$) with Al. To allow for a possible disorder of Ni and Al at both positions

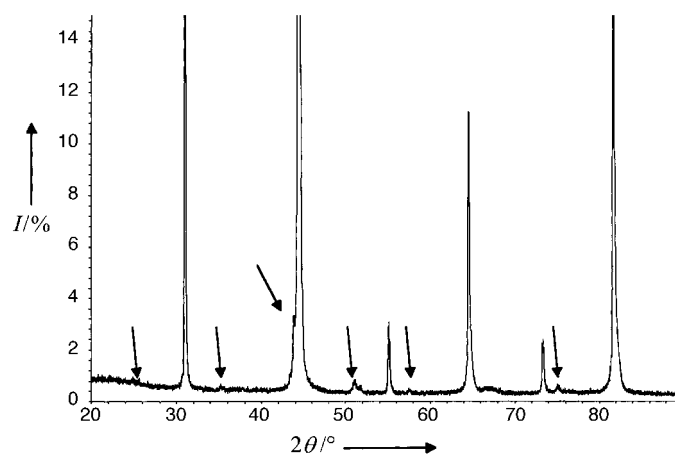


Figure 5. Section of the powder diagram of **3** after annealing at $1000^\circ C$. The reflections of the Ni_3Al phase are indicated by arrows.

Table 1. Observed (I_{exp}) and calculated (I_{calc}) intensities in the powder diagram of **3**.

(hkl)	I_{exp}	I_{calc}
(100)	14	14
(110)	100	100
(111)	3	3
(200)	16	15
(210)	3	3
(211)	28	28
(220)	9	9
(300)	< 1	< 1
(221)	1	1
(310)	16	15
(311)	< 1	< 1

the two positions were additionally occupied with Al and Ni, respectively. The refinement of the occupancy factors was carried out under the specification of full occupancy of both positions. The data converged for $R_B = 0.023$, $\chi^2 = 1.4\%$ (for all measured points) and $R_{WP} = 0.111$; the lattice parameter is 288.4(1) pm. The refinement of the crystal structure refinement gave a mixed occupancy of Ni and Al at both positions.

For the 1a position there were occupancies of 0.92(3) Ni and 0.08(3) Al. The 1b position is occupied with 0.97(2) Al and 0.03(2) Ni. This gives a composition of $Ni_{0.95}Al_{1.05}$ for the β -nickel aluminide.^[19] The evaluation of the X-ray data thus shows that **3** is a β -nickel aluminide contaminated with a small amount of α -nickel aluminide.

The particle size was determined on the basis of the data shown in Figure 4, and LaB_6 served as reference compound. The primary particle sizes were calculated according to the Scherrer method, and the (100), (110), (200), and (211) reflections were used for the calculation. A mean primary particle size of $\varnothing = 4 \text{ nm}$ was obtained.

The NiAl material **2** was characterized by SEM. Because of its small particle size of 2–4 nm (TEM) **2** is highly sensitive towards oxidation and was therefore annealed at $500^\circ C$ under H_2 before transfer into the SEM apparatus. The SEM image (Figure 6, original enlargement: $96\times$) of the pretreated NiAl powder shows differently sized particles (ca 150–500 μm), which have, however, no conspicuous, that is ordered,

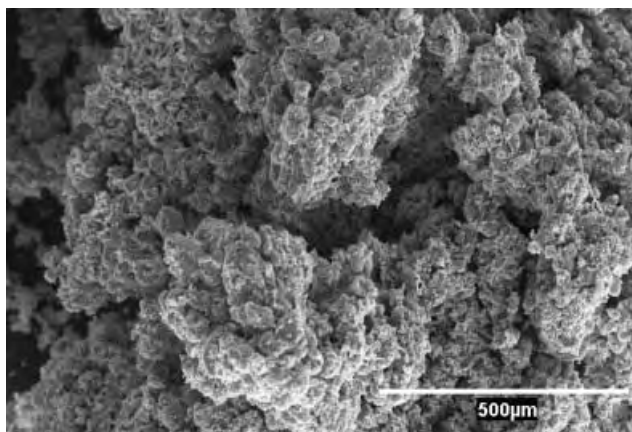


Figure 6. SEM image of **2** (after annealing at 500 °C).

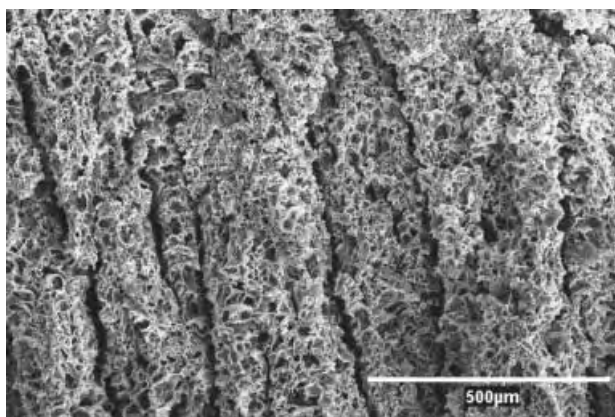


Figure 7. SEM image of **3**.

structure. The already slightly sintered NiAl powder annealed at 1000 °C exhibited, in contrast, channel-like trenches (Figure 7, original enlargement: $96\times$).

By changing the mass ratio $[\text{Ni}(\text{cod})_2]/\text{AlEt}_3$ from 1:1 to 3:1 the synthesis described here produces α -nickel aluminide Ni_3Al . The reaction with GaEt_3 , $[\text{Fe}(\text{C}_5\text{H}_5)(\text{cod})]$, and $[\text{Ce}(\text{C}_5\text{H}_5)_3]$ gives the ternary aluminides NiGaAl , FeNiAl , and CeNiAl (see Experimental Section).^[16]

Experimental Section

Synthesis of 2: An equimolar amount of AlEt_3 (3.42 g) was added to a solution of $[\text{Ni}(\text{cod})_2]$ (8.24 g, 30 mmol) in toluene (100 mL) under an inert atmosphere. After transfer to an autoclave and pressurization with H_2 to 5–10 MPa the reaction mixture was stirred at room temperature for 72 h. A clear solution was formed from which a solid separated. After removal of the solvent and drying in high vacuum (10^{-2} Pa), the black, highly air-sensitive crude product **1** was isolated.^[20] Compound **1** was hydrogenated at 200 °C and then annealed under argon at 300 °C. Elemental analysis of **2** (%): Ni 67.57, Al 30.69, C 0.02, H 0.02. Yield: 2.49 g (96.8% of the theoretical amount).

Analysis of 2: XRD (STADI-P, Stoe, with primary monochromator): $\text{Cu}_{\text{K}\alpha 1}$ radiation (1.540598 Å), linear site-sensitive detector. The data for the Rietveld analysis were collected in the region $2\theta = 20\text{--}130^\circ$ with an intercept length of 0.01° . The samples were measured in sealed quartz glass capillaries.

IR (Magna 750, Nicolet): KBr, resolution 4 cm^{-1} ; $\bar{\nu} = 604\text{vs}$, 727s, 752s, 918w, 948m, 985s, 1171w, 1261w, 1369w, 1389w, 1444m, 1591w, 2858m, 2892m, 2922m cm^{-1} .

DSC/TG/MS (STA 449 C, Netzsch-Gerätebau, coupled with a quadrupole mass spectrometer ThermoStar 442, Balzers): measurement range 30–1500 °C, heating rate $10^\circ\text{C min}^{-1}$, Argon.

SEM investigations were carried out with a Hitachi PC-controlled apparatus, Type S8500N which was equipped with an EDX detector from Oxford Instruments. For the SEM morphology investigations it was sufficient to mount the samples on a conducting carbon pad.

Synthesis of ternary aluminides as exemplified of Ga-doped NiAl 5: AlEt_3 (3.09 g, 27.1 mmol) and GaEt_3 (1.1 g, 7 mmol) were added to a sample of $[\text{Ni}(\text{cod})_2]$ (9.27 g, 34.07 mmol) in toluene (100 mL) under an inert atmosphere. After transfer into an autoclave and pressurization with H_2 (5 MPa), the reaction mixture was stirred for 16 h at 130 °C. After precipitation of the reaction mixture, removal of the solvent, and drying in high vacuum (10^{-2} Pa), the black, highly air-sensitive crude product **4** was isolated.^[21] Product **4** was then hydrogenated for 24 h at 390 °C without pressurization to give the final product **5**. Elemental analysis of **5** (%): Ni 60.96, Al 19.89, Ga 14.40, C 0.53, H 0.08. Yield: 3.21 g (99.7% of theoretical amount).

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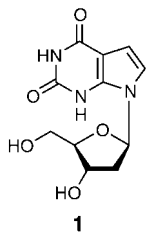
worse R_B value of 0.054. The secondary phase Ni_3Al was also considered in the refinement. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, 6344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666); e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-412238.

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- [21] Elemental analysis of **4** (%): Ni 59.7, Al 21.8, Ga 13.8, C 6.7, H 0.9.

7-Deaza-2'-deoxyxanthosine Dihydrate Forms Water-Filled Nanotubes with C–H...O Hydrogen Bonds**

Frank Seela,* Thomas Wiglenda, Helmut Rosemeyer, Henning Eickmeier, and Hans Reuter*

Inspection of an assembly of 7-deaza-2'-deoxyxanthosine dihydrate (**1**·2H₂O) molecules^[1] within a crystal discloses interesting structural features: Besides an intramolecular hydrogen bond (N3–H...OH–5'), an array of further hydrogen bonds stabilizes a supramolecular aggregate of four molecules of **1**. This arrangement results in the formation of an almost flat tetramer (Figure 1) with an oval cavity of approximate dimensions $9.5 \times 6.5 \times 3.0$ Å (± 0.5 Å). A pile of completely stacked tetramers forms a columnar nanotube-like structure (Figure 2).



The synthesis of **1**^[2] was performed as described previously.^[3] It was crystallized from *i*PrOH/H₂O/MeOH (3/1/1), which was slightly acidified with glacial acetic acid, as a dihydrate in the monoclinic space group $P2_1$ (see Supporting Information).^[4] The structure shows that **1** exists in the 2,4-dioxo form in the solid state (Figure 3); both oxo substituents lie slightly out of the ring plane.

The torsion angle χ^1 (O4'–C1'–N9–C4),^[5] which defines the orientation of the base relative to the sugar group (*syn/anti*),

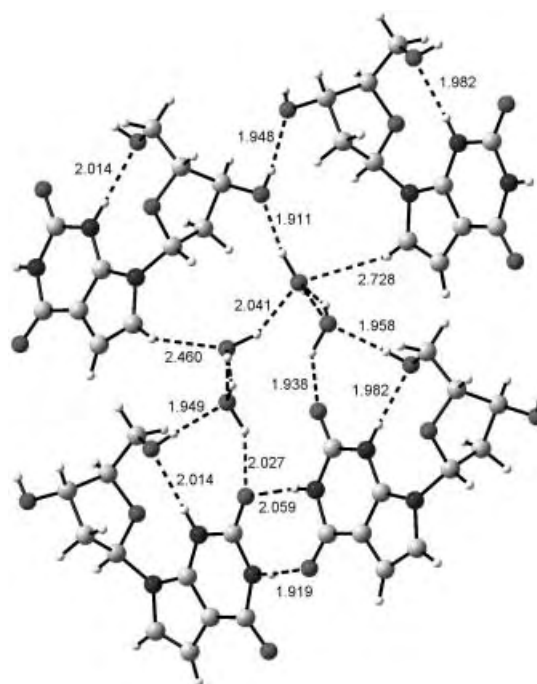


Figure 1. Length of the hydrogen bonds in a water-containing tetramer of **1**.

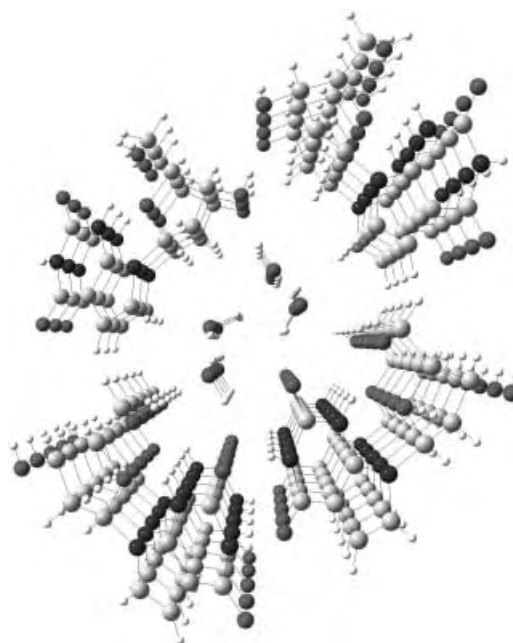


Figure 2. Nanotube of stacked tetramers (see Figure 1).

amounts to 61.9° ; thus the nucleoside **1** adopts the *syn* conformation. A literature survey^[6] of nearly 300 X-ray structures of nucleosides reveals that **1** belongs to the minor group of about 50 structures showing this N-glycosylic *syn* conformation. The *syn* conformation around the N-glycosylic bond is unusual for 7-deazapurine nucleosides.^[7] In the case of **1** it is fixed by an intramolecular hydrogen bond between the H atom on N3 and the O atom of the 5'-OH group (separation 1.98 Å)^[8] forcing the exocyclic 5'-CH₂OH moiety into the +sc[(+)*g*] conformation with a torsion angle γ of 52° for C3'–C4'–C5'–O5'. The sugar ring adopts the $^2T_3$ ("south") con-

[*] Prof. Dr. F. Seela, Dipl.-Chem. T. Wiglenda, Dr. H. Rosemeyer
Laboratorium für Organische und Bioorganische Chemie
Institut für Chemie, Universität Osnabrück
Barbarastrasse 7, 49069 Osnabrück (Germany)
Fax: (+49) 541-969-2370
E-mail: Frank.Seela@uni-osnabrueck.de

Prof. Dr. H. Reuter, H. Eickmeier
Anorganische Chemie II
Institut für Chemie, Universität Osnabrück
Barbarastrasse 7, 49069 Osnabrück (Germany)
Fax: (+49) 541-969-3323
E-mail: hreuter@uni-osnabrueck.de

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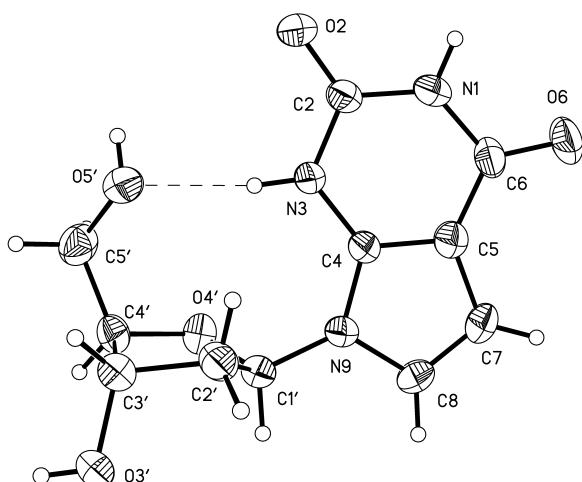


Figure 3. Molecular structure of $1 \cdot 2\text{H}_2\text{O}$. The intramolecular hydrogen bond that stabilizes the *syn* conformation is shown as a dashed line. Displacement ellipsoids for the atoms are drawn at the 50% probability level and H atoms are shown as spheres of an arbitrary size.

formation with a puckering amplitude $\phi_m = 35.9^\circ$ and a pseudorotation phase angle $P = 155.1^\circ$.^[9] These conformational parameters are typical for most nucleosides in the *syn* conformation.^[6] The discrete structure of **1** is maintained in aqueous solution, as determined by analysis of the vicinal ^1H , ^1H NMR coupling constants of the sugar moiety of **1** as well as by $[\text{H}, ^1\text{H}]$ -NOE difference spectroscopy.^[10]

Tetrameric assemblies of guanine and isoguanine derivatives containing various mono- or divalent cations have been identified as a fundamental structural element of supramolecular materials.^[11] Such tetramers also form the elementary unit of guanine, isoguanine, and 7-deazaisoguanine-rich telomeric quadruplex DNA and RNA and of the so-called guanine wires.^[12] Each oval-shaped tetramer cavity contains four water molecules of which two at any one time are interconnected by hydrogen bonds. The four guest molecules form a chain that bridges the nucleoside hosts. Two conventional types of hydrogen bond and an unconventional type were detected: conventional hydrogen bonds exist between the 3'- and 5'-OH groups of **1** and the O atom of a water molecule ($\text{O}-\text{H} \cdots \text{O}$) and between the O2 atom of **1** and a H atom of a water molecule ($=\text{O} \cdots \text{H}-\text{O}$). The O atoms of two of the H_2O molecules form unconventional hydrogen bonds to corresponding H atoms on C8 (Figure 1; 2.460 and 2.728 Å).^[13] Both water oxygen atoms involved exhibit different coordination: one exhibits a distorted tetrahedral, the other one a distorted trigonal bipyramidal coordination sphere. As can be seen from Figure 2, all the H_2O molecules of the same type are arranged strictly in line along the nanotube.

The ability of the pyrrole hydrogen atoms of **1** to form attractive bonds such as hydrogen or anti-hydrogen^[14] bonds is of particular importance for the structure, solvation, and stability of nucleic acids^[15] containing such nucleoside units. This also concerns other analogous nucleosides, such as 7-deaza-2'-deoxyisoguanosine.^[16] Being isosteric to the regular purine nucleosides, such base-modified nucleosides are well accommodated into a regular B-DNA double helix^[17] and

have been incorporated into triplex-forming oligonucleotides.^[18] The pyrrole hydrogen atoms C7-H and C8-H are exposed to the major groove of the helix and are thus contact points for solvation by water molecules. Despite the common opinion, DNA double strands carrying stretches of 7-deazapurine bases do not necessarily contain a hydrophobic major groove, but might still bind water molecules in a similar manner as described for conventional DNA built-up from corresponding purine bases.

One also has to take into account the potential of such nucleosides to form base-pair motifs through the participation of $\text{C8/C7}-\text{H} \cdots \text{N/O}$ bonds. Analogous attractive $\text{C}-\text{H} \cdots \text{O/N}$ interactions have been described for U-U base pairs (the so-called Kalkutta base pair), A-A base pairs, and within Z-DNA from X-ray analysis of corresponding oligonucleotides and quantum chemical computations of model base pairs.^[15] Despite the fact that the energy contribution of $\text{C}-\text{H} \cdots \text{X}$ bonds is low compared to that of standard hydrogen bonds,^[15c] they have been postulated for the recognition of pyrimidine bases in a parallel DNA triple-helix motif^[19] as well as for base pairs formed between guanine and ethenoadenine.^[20] Such hydrogen bonding might also exist in nucleic acid duplexes incorporating other 7-deazapurine nucleosides. In this context the base-pairing properties of **1** as well as its potential of forming high molecular weight aggregates, such as triplexes or tetramers, at the oligonucleotide level are under current investigation. Additionally, compounds such as **1** allow the storage or the transport of various hydrophilic molecules.^[21]

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RNA Two-State Conformation Equilibria and the Effect of Nucleobase Methylation**

Claudia Höbartner, Marc-Olivier Ebert, Bernhard Jaun, and Ronald Micura*

The constitutional diversity of RNA is impressively reflected in more than 90 chemically modified nucleosides.^[1, 2] It was reported recently that the modified nucleosides of a human mitochondrial tRNA^{Lys} are required for the formation of the correct cloverleaf three-dimensional structure.^[3] In contrast, the corresponding unmodified in vitro transcript did not fold into a cloverleaf but into an extended bulged hairpin. To the best of our knowledge, these studies provide the first and so far only experimental data that document the significant influence of nucleoside modifications on RNA folding. These results encouraged us to investigate systematically the effect of nucleobase methylation in short palindromic oligoribonucleotide duplexes. We found that the replacement of single nucleosides with the corresponding methylated counterparts, such as 1-methylguanosine (m¹G), N²,N²-dimethylguanosine (m²G), N⁶,N⁶-dimethyladenosine (m⁶A), or 3-methyluridine (m³U), led to the formation of a hairpin rather than of a duplex structure.^[4] These remarkable changes in the secondary structure motif form the basis of our investigations. Herein we report on single-stranded oligoribonucleotides that exist in monomolecular two-state conformation equilibria. By methylation of selected nucleobases, it is possible to shift these equilibria to a significant extent.

The methylation pattern of the studied sequences corresponds to the naturally occurring helix 45 loop located at the 3'-end of ribosomal RNA of the small subunit (SSU) (Figure 1).^[5] The two successive m⁶A nucleosides within the four-membered loop are conserved almost universally in bacteria and eukaryotes. These modified adenosines are functionally significant; however, the exact reason for their methylation is not yet understood. We have chosen 5'...CCm²GGm⁶A-m⁶AGG...3' as a lead sequence for a comparison of the conformation of methylated versus nonmethylated sequence constructs (Table 1, Figure 2). Two questions are important in the sequence design. First, is a complementary sequence partition such as 5'...CCUUC...3' able to break up the nonmethylated stem-loop structure of 5'...CCGGAAGG...3'?

[*] Dr. R. Micura, DI C. Höbartner
Institute of Organic Chemistry, Leopold Franzens University
Innrain 52a, 6020 Innsbruck (Austria)
Fax: (+43) 512-5072892
E-mail: ronald.micura@uibk.ac.at
Dipl.-Chem. M.-O. Ebert, Prof. Dr. B. Jaun
Laboratory of Organic Chemistry
Universitätsstrasse 16, 8092 Zürich (Switzerland)

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

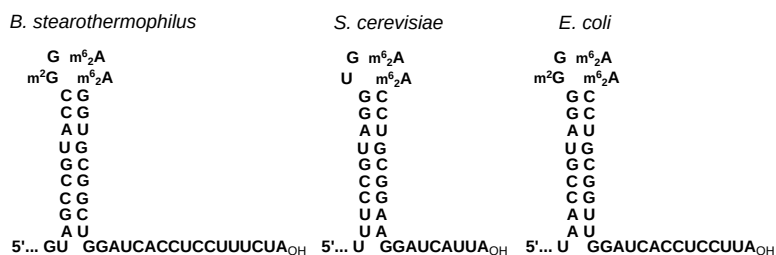


Figure 1. Selected helix 45 motifs located at the 3'-end of rRNA of the SSU. The successive dimethylated m⁶A nucleotides within the loop are conserved in most organisms. The reason for the methylation is unclear. m²G = N²-methylguanosine.

Second, if so, does the methylation according to the helix 45 pattern 5'...CCm²GGm⁶Am⁶AGG...3' cause a reconstitution of the original stem-loop structure?

Figure 2 shows a set of sequences that is ideal to investigate these questions experimentally.^[6] In principle, both the non-methylated sequence **1** and the methylated sequence **2** are able to adopt two different conformations **1'/1''** and **2'/2''**, respectively (Figure 2a). These conformations are easily assigned by comparison with a pair of appropriate references (Figure 2b). The reference sequences **1a/1b** and **2a/2b** represent short sections of sequences **1** and **2** that are only able to adopt a single conformation. This defined conformation of **1a**, **1b** (and **2a**, **2b**) corresponds to one of the two

possible conformations **1'** or **1''** of sequence **1** (and **2'** or **2''** of sequence **2**).

We used ¹H NMR spectroscopy to determine the conformations of **1** and **2** (Figure 3). The NH signals in the ¹H NMR spectrum of **1** show characteristic slow H/D-exchange; the spectrum displays the NH resonances as measured for the individual reference sequences **1a** and **1b** in a 25:75 ratio.^[7] This clearly shows that sequence **1** exists in a conformation equilibrium between **1'** and **1''** at 298 K.^[8] In contrast, the methylated sequence **2** gives rise to the NH resonances of reference **2a** only, which indicates that

sequence **2** exists exclusively in a single conformation (**2'**). It is thus clear that methylation forces the former formation of the unfavorable secondary structure.

The approach presented allows an estimation of the thermodynamic properties of base pairing of the competing substructures within sequences **1** and **2**. The thermodynamic parameters of references **1a/1b** and **2a/2b** were derived from UV melting profiles (Figure 4).^[9] A comparison of the *T_m* values and the corresponding Δ*G*^{298 K-UV} values of the reference substances can be used to predict qualitatively the position of the conformation equilibrium of **1** or **2**. However, we wish to stress that the references do not necessarily represent the precise thermodynamic behavior of the corre-

Table 1. Methylated and nonmethylated oligoribonucleotides that contain a helix 45 sequence motif of rRNA; melting temperatures *T_m*, thermodynamic data of double-helix formation derived from UV melting profiles, conformation equilibrium constants derived from ¹H NMR spectra, mass spectral data.^[a-e]

No.	Base sequences	<i>T_m</i> ^[a] [°C]	Thermodynamic data of double-helix formation ^[a, b]			Conformation equilibrium constant ^[c, d]		Mass spectral data ^[e]	
			Δ <i>H</i> ^o [kcal mol ⁻¹]	Δ <i>S</i> ^o [cal mol ⁻¹ K ⁻¹]	Δ <i>G</i> _{298 K} ^o [kcal mol ⁻¹]	<i>K</i> _{conformer} ^{298 K-NMR}		<i>M</i> _{calcd.}	<i>M</i> _{obs.}
1	GACCGGAAGGUCCGCCUUC	78.0				3.0	(25:75)	6356.8	6355.9
1a	GACCGGAAGGUCC	77.7	−54.7	−157.1	−7.9			4178.6	4178.1
1b	CGGAAGGUCCGCCUUC	73.3	−55.0	−160.0	−7.3			5377.2	5376.3
2	GACCM ² GGm ⁶ Am ⁶ AGGUCCGCCUUC	72.7	−48.3	−140.7	−6.3	< 0.02	(> 98: < 2)	6427.0	6426.4
2a	GACCM ² GGm ⁶ Am ⁶ AGGUCC	72.7	−49.8	−145.1	−6.5			4248.7	4247.9
2b	Cm ² GGm ⁶ Am ⁶ AGGUCCGCCUUC	54.0	−34.5	−104.2	−3.4			5447.4	5445.0
3	GACCGGAAGGUCCGCCUUCG	81.2				5.7	(15:85)	6702.0	6702.1
4	GACCM ² GGm ⁶ Am ⁶ AGGUCCGCCUUCG	72.4	−41.9	−122.0	−5.5	< 0.02		6772.2	6771.8
5	GACCGGAAGGUCCUUCUUC	78.2				1.2	(45:55)	6318.8	6318.3
5a	GACCGGAAGGUCCU	77.9	−56.4	−161.4	−8.3			4179.6	4178.6
5b	CGGAAGGUCCUUCUUC	70.5	−48.0	−140.8	−6.0			5339.2	5339.0
6	GACCM ² GGm ⁶ Am ⁶ AGGUCCUUCUUC	73.2	−49.3	−142.5	−6.8	< 0.02		6388.9	6386.8
6a	GACCM ² GGm ⁶ Am ⁶ AGGUCCU	73.2	−48.8	−141.1	−6.7			4249.7	4248.8
6b	Cm ² GGm ⁶ Am ⁶ AGGUCCUUCUUC	41.6	−34.7	−108.4	−2.4			5409.3	5408.1
7	GACCGGAAGGUCC _{E3} CCUUC	70.8				1.5	(40:60)	6130.7	6131.0
7a	GACCGGAAGGUCC	72.4	−51.3	−149.3	−7.1			3874.1	3874.9
7b	CGGAAGGUCC _{E3} CCUUC	68.2	−62.4	−183.3	−7.7			5151.1	5152.0
8	GACCM ² GGm ⁶ Am ⁶ AGGUCC _{E3} CCUUC	67.5	−50.9	−149.2	−6.4	< 0.02		6200.9	6200.6
8a	GACCM ² GGm ⁶ Am ⁶ AGGUCC	64.9	−39.5	−116.6	−4.7			3945.2	3945.5
8b	Cm ² GGm ⁶ Am ⁶ AGGUCC _{E3} CCUUC	40.6	−31.4	−99.2	−1.8			5221.3	5222.5
9	GAGGGGAACCUCCGGUUC	81.8				19.0	(5:95)	6436.9	6436.5
9a	GAGGGGAACCUCC	67.0	−43.9	−129.6	−5.3			4178.6	4176.7
9b	GGGAACCUCCGGGUUC	79.9	−48.4	−138.4	−7.1			5417.3	5418.2
10	GAGGm ² GGm ⁶ Am ⁶ ACCUCCGGGUUC	61.0	−40.0	−120.0	−4.3	< 0.02		6507.0	6504.5
11	GAGGGGAACCUCCGGGUUC	73.9				4.0	(20:80)	6131.7	6130.4
11a	GAGGGGAACCUCC	67.0	−43.9	−129.6	−5.3			4178.6	4176.7
11b	GGAAACCUCCGGGUUC	71.7	−43.7	−127.9	−5.6			4766.9	4766.1
12	GAGGm ² GGm ⁶ Am ⁶ ACCUCCGGGUUC	60.7	−40.1	−119.5	−4.5	< 0.02		6201.8	6199.0

[a] 2 μM, 150 mM NaCl, 10 mM Na₂HPO₄, pH 7.0. [b] Δ*H*^o and Δ*S*^o were derived from *a*/*T*-plots by curve fitting; see ref.[9]. [c] 0.2 mM; 25 mM sodium arsenate buffer, pH 7.4, 298 K, H₂O/D₂O 9:1. [d] Conformer ratio (%). [e] MALDI-TOF or ESI mass spectrometry was used.

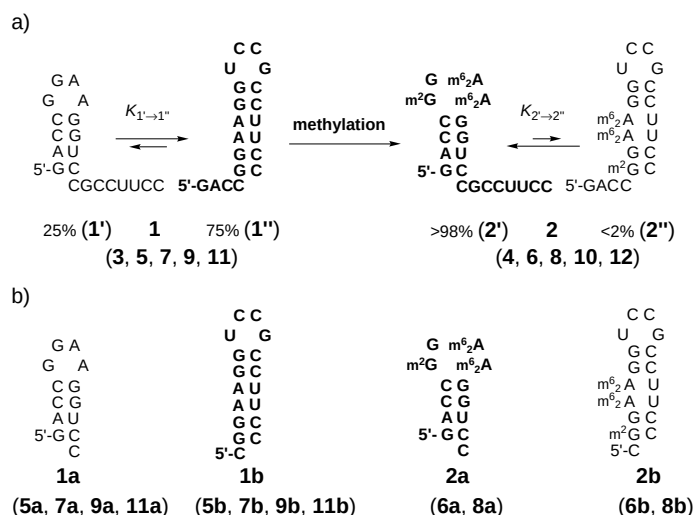


Figure 2. a) General approach for the investigation of monomolecular RNA two-state conformation equilibria and the equilibrium shifts induced by nucleobase methylation. This example illustrates sequence constructs that comprise a helix 45 motif (compare Figure 1). Both **1** and **2** are, in principle, able to adopt two different conformations (**1'**/**1''** and **2'**/**2''**). b) With the corresponding set of references (**1a/1b** and **2a/2b**), the conformation was easily determined by means of ^1H NMR spectroscopy (compare Figure 3). At 298 K, the nonmethylated sequence **1** exists in a two-state conformation equilibrium (**1'**/**1''** 25:75). The position of the equilibrium is sensitive to sequence variations (compare equilibrium constants for **3**, **5**, **7**, **9**, and **11** in Table 1). Upon methylation, the equilibrium is shifted in the direction of a single conformer (>98% **2'**), which corresponds to the former unfavorable conformer.

sponding substructures within **1** or **2**, and moreover, that the determination of ΔG derived from UV melting curves is subject to a 2 to 5% error. The error value for references **1a/1b** is ± 0.2 – 0.4 kcal mol $^{-1}$ and therefore within the order of the equilibrium to be estimated. The energy difference $\Delta\Delta G_{1a,1b}^{298\text{ K}-\text{UV}}$ of $+0.6$ kcal mol $^{-1}$ derived for the individual references favors **1a** over **1b** as the more stable hairpin, and allows an estimate of $K_{1'-1''}^{298\text{ K}-\text{UV}}$ (ca. 0.37). However, the exact position of the equilibrium can only be determined from the ^1H NMR spectrum and in case of sequence **1**, is clearly in favor of conformation **1''** ($K_{1'-1''}^{298\text{ K}-\text{NMR}} = 3.0$).^[10] A $\Delta\Delta G_{2a,2b}^{298\text{ K}-\text{UV}}$ value of $+3.1$ kcal mol $^{-1}$ is derived from the UV data of methylated references **2a** and **2b** and suggests a $K_{2'-2''}^{298\text{ K}-\text{UV}}$ of 0.0053. These values further corroborate that **2'** is the dominant conformation of sequence **2**, as determined from the ^1H NMR spectrum ($K_{2'-2''}^{298\text{ K}-\text{NMR}} < 0.02$; Figure 3b). We point out that the methylations destabilize **1'** relative to **2'** and, much more prominently, **1''** relative to **2''**. At a molecular level, this can be explained by the disruption of the GA sheared base pair for **1'** relative to **2'**, and the disruption of two Watson–Crick base pairs for **1''** relative to **2''**.

The observations described above are not limited to sequences **1** and **2**. To understand further the properties of two-state conformation equilibria and the impact of methylation on these equilibria, we investigated the related sequences **3** to **12** (compare Table 1 and Supporting Information). The oligonucleotides **3** and **4** differ from **1** and **2** by an additional guanosine at the 3'-end. Consequently, the equilibrium of the nonmethylated sequence **3** is further shifted

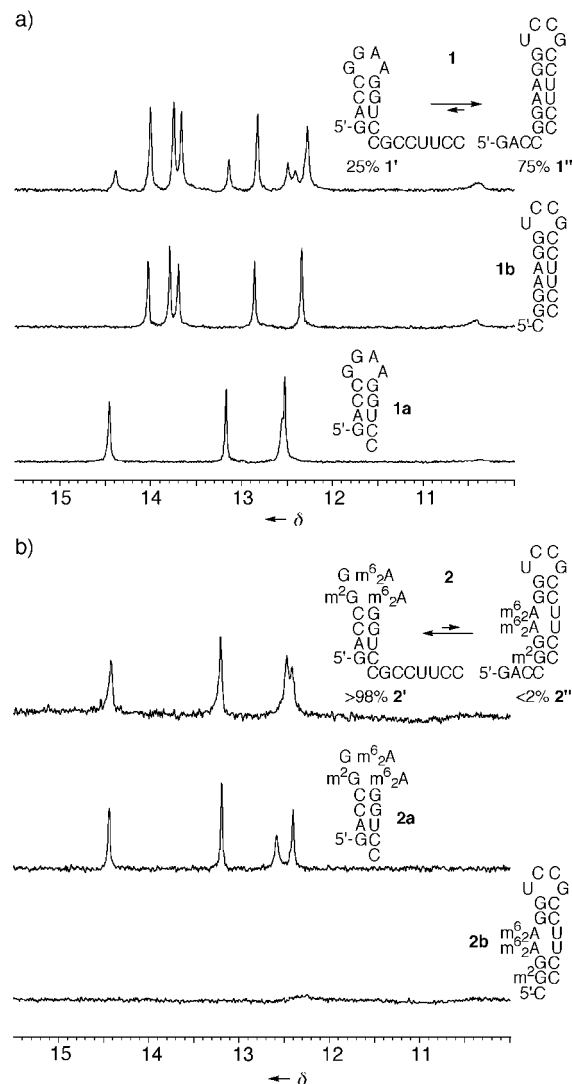


Figure 3. Determination of RNA conformation equilibria by means of ^1H NMR spectroscopy. a) The ^1H NMR spectrum of **1** shows signals according to the NH-resonances of both references **1a** and **1b** and ascertains a 25:75 equilibrium of **1'** and **1''** (for sample conditions see ref. [7]). b) In contrast, the ^1H NMR spectrum of **2** reflects the NH resonances corresponding to reference **2a**. Reference **2b** does not show any NH resonances at 298 K—evidence for the conformation depicted was obtained from the UV melting profile (compare Figure 4).

towards the UCCG-hairpin conformation ($K_{3'-3''}^{298\text{ K}-\text{NMR}} = 5.7$). The equilibrium of the methylated sequence remains reversed; **4** exclusively adopts the $\text{m}^2\text{GGm}^6_2\text{Am}^6_2\text{A}$ stem-loop structure, which corresponds to **2'** ($K_{4'-4''}^{298\text{ K}-\text{NMR}} < 0.02$).

The oligonucleotides **5** and **6** differ from **1** and **2** by a two-nucleoside exchange (C13G14 by U13U14). Therefore, the two-state conformation equilibrium of sequence **5** no longer reflects the competition between a GNRA and a UNCG hairpin, both of which are known to adopt extraordinarily stable secondary structures.^[11] In **5**, the latter sequence segment is replaced by UCUU. This exchange causes a conformation equilibrium in which conformer **5''** is only slightly favored over **5'** ($K_{5'-5''}^{298\text{ K}-\text{NMR}} = 1.2$). Upon methylation, the position of the equilibrium is pushed entirely to the $\text{m}^2\text{GGm}^6_2\text{Am}^6_2\text{A}$ hairpin **6'** ($K_{6'-6''}^{298\text{ K}-\text{NMR}} < 0.02$).

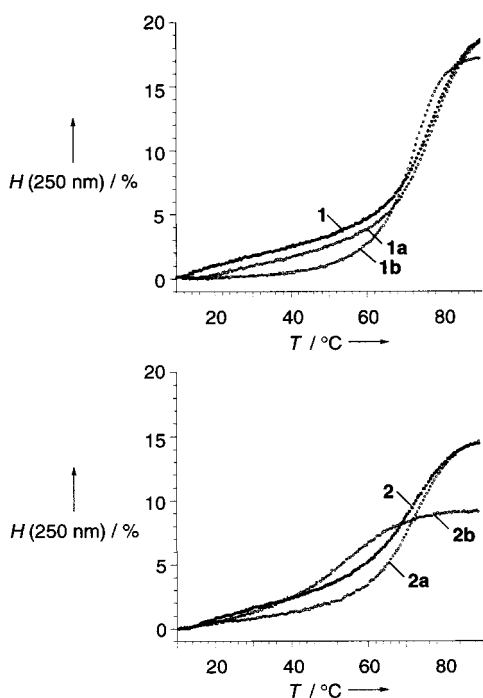


Figure 4. UV melting profiles: a) GACCGGAAGGUCCGCCUUC **1** ($T_m = 78.0^\circ\text{C}$), references GACCGGAAGGUCC **1a** ($T_m = 77.7^\circ\text{C}$), CGGAAGGUCCGCCUUC **1b** ($T_m = 73.3^\circ\text{C}$). b) GACCM²GGm⁶₂Am⁶₂AGGUCCGCCUUC **2** ($T_m = 72.7^\circ\text{C}$), references GACCM²GGm⁶₂Am⁶₂AGGUCC **2a** ($T_m = 72.7^\circ\text{C}$), CM²GGm⁶₂Am⁶₂AGGUCCGCCUUC **2b** ($T_m = 54.0^\circ\text{C}$); c = 2 μM , 150 mM NaCl, 10 mM Na₂HPO₄, pH 7.0.

The oligonucleotides **7** and **8** differ from **1** and **2** again by a two-nucleoside exchange within the original UCCG sequence segment; C13G14 is replaced by non-nucleotide linker units, namely bis(triethylene glycol) phosphate (E₃E₃).^[12] Interestingly, this modification does not cause a significant destabilization of **1'**. The constants of the conformation equilibria of **7** and **8** are comparable to those of **1** and **2**.

The oligonucleotides **9/10** and **11/12** have different loop-closing base pairs than the sequences discussed above (C/G converted into G/C; compare also Figure 1). The sequence pair of **9/10** represents a conformation switch induced by methylation ($K_{9-9'}^{298\text{K-NMR}} = 19$ and $K_{10-10'}^{298\text{K-NMR}} < 0.02$).

The ability of RNA molecules to adopt two (or more) stable conformations is generally discussed in terms of RNA tertiary structure and is often related to the concept of molecular switches.^[13, 14] The latter implies that the conformation of a single molecule is forced into an alternative one by an extrinsic stimulator, for example, the addition of Mg²⁺,^[14a] the addition of a complementary oligonucleotide,^[14b] or a variation in the pH.^[14c] At the secondary structure level and in the absence of extrinsic factors, monomolecular conformation equilibria have been postulated,^[15] but to the best of our knowledge, the coexistence of conformers in equilibrium has not yet been verified experimentally for shorter RNA sequences. Our approach now allows the thorough investigation of monomolecular equilibria of competing stem-loop structures within single-stranded RNA molecules: that is, first, the identification of the base sequence prerequisites and the allowed sequence variety; second, the determination of

the pairing properties of the competing substructures; and third, the extraction of the thermodynamics for the conformation equilibria. Furthermore, we consider the investigation of such equilibria fundamental for an understanding of the early stages of the RNA-folding processes. Equilibria of this kind may reflect the status of branching into different folding pathways.^[16]

Beyond that, with the sequence design that includes the helix 45 motif, we have addressed equilibrium shifts ("switches") induced by methylation of the nucleobases. In particular, tetra-, penta-, and hexanucleotide sections that are complementary to the helix 45 loop region are found in the nucleotide sequences of rRNA.^[17] These complementary sections may well constitute folding traps that are avoided upon methylation. This might be a reason for the highly conserved methylation pattern of helix 45 in the SSU of rRNA.^[18]

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Iron-Catalyzed Cross-Coupling Reactions of Alkyl-Grignard Reagents with Aryl Chlorides, Tosylates, and Triflates**

Alois Fürstner* and Andreas Leitner

Classical cross-coupling processes such as the Kumada–Corriu, Negishi, Stille, or Suzuki reaction are of utmost importance for modern organic synthesis.^[1] These transformations are usually catalyzed by palladium or nickel complexes, although no inherent restriction to these late transition metals exists. Aryl iodides and bromides are the best substrates; only recently have special ligands been designed that allow the scope of these methods to be extended to aryl chlorides.^[2] Aryl triflates represent yet another class of suitable starting materials, whereas less expensive sulfonates have hardly been used so far because of their lack of activity in most cases.^[3]

Herein we describe initial studies on the development of an alternative cross-coupling procedure which allows the attachment of alkyl groups to arenes in a very efficient way.^[4] This method is distinguished by a number of notable advantages:

- 1) expensive noble metal catalysts are replaced by cheap, stable, commercially available and toxicologically benign iron salts
- 2) aryl chlorides and triflates provide a priori better results than the corresponding bromides or iodides
- 3) aryl tosylates turned out to be suitable starting materials as well
- 4) the reaction is performed under “ligand-free” conditions
- 5) the reaction times are usually very short.

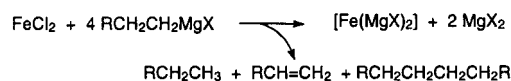
Although iron salts were proposed as catalysts for cross-coupling reactions by Kochi et al. as early as 1971,^[5] they attracted little attention in the following decades.^[6] Their scope remained essentially limited to reactions of Grignard reagents with *alkenyl* halides.^[6, 7] Successful applications to other types of substrates, in particular to *aryl* halides, have not been reported. Moreover, the mechanism of the iron-catalyzed reactions remained rather obscure, whereas detailed insights into most of the prominent palladium-catalyzed processes have been gained over the years.^[1] It has been proposed that Fe⁰ or Fe^I species constitute the catalytically relevant intermediates,^[5] although no secured information as to their structure or mode of action could be obtained. Alternatively, “super-ate” complexes of Fe^{II} have been suggested as the active species.^[8]

Taking recent advancements in the field of “inorganic Grignard reagents” into consideration,^[9] however, these hypotheses seem to be highly unlikely and called for a re-evaluation of iron-catalyzed cross-coupling chemistry. It is now well established that FeCl₂ reacts with *four* equivalents of

[*] Prof. Dr. A. Fürstner, Dipl.-Ing. A. Leitner
Max-Planck-Institut für Kohlenforschung
45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2994
E-mail: fuerstner@mpi-muelheim.mpg.de

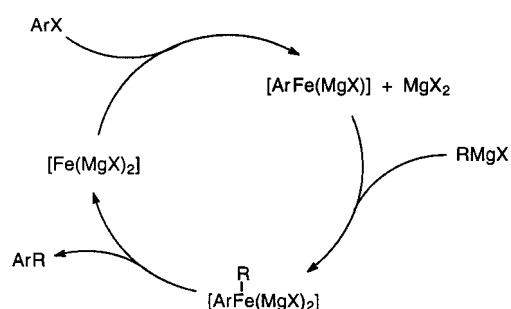
[**] This work was supported by the Deutsche Forschungsgemeinschaft (Leibniz program) and the Fonds der Chemischen Industrie. We thank Prof. B. Bogdanović for helpful discussions.

RMgX to give a new species of the formal composition $[\text{Fe}(\text{MgX})_2]$.^[10] This implies that the reduction process does not stop once a zerovalent iron species “Fe⁰” is formed, but rather generates Fe^{-II} centers (Scheme 1),^[9, 11] which are



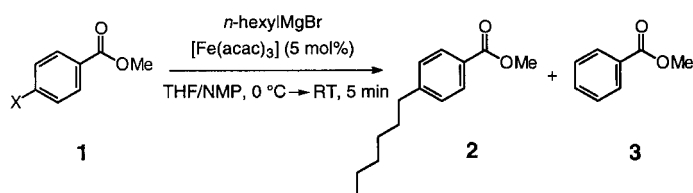
Scheme 1. Known stoichiometry for the formation of an inorganic Grignard reagent of iron.^[9, 11]

capable of oxidatively inserting into aryl halides due to their highly nucleophilic character.^[11, 12] We anticipated that the ensuing Fe⁰ complexes might again be alkylated by a suitable Grignard reagent.^[13] Subsequent reductive coupling should then form the desired product and regenerate the catalytically active $[\text{Fe}(\text{MgX})_2]$ species (Scheme 2).^[10, 14]



Scheme 2. Proposed formal catalytic cycle for the iron-catalyzed cross-coupling process.^[14]

Initial attempts to verify this concept using aryl iodide **1a** (X = I; Scheme 3) or aryl bromide **1b** (X = Br) were only partly successful. Although we were able to detect the cross-coupling product **2** in the reaction mixture, the reduction of the substrates with formation of compound **3** prevailed (Table 1). In marked contrast, however, the use of chloride **1c** as the starting material led to the almost quantitative formation of the desired alkylbenzoic acid ester **2**; notably, the



Scheme 3. Optimization of the iron-catalyzed cross-coupling reaction of substrate **1**, (see Table 1). NMP = *N*-methylpyrrolidone.

Table 1. Screening of different substrates in the iron catalyzed cross coupling reaction depicted in Scheme 3.

Entry	X	Yield [GC, %]	2	3
1	I	27	46	
2	Br	38	50	
3	Cl	> 95	–	
4	OTf	> 95	–	
5	OTs	> 95	–	

conversion is quantitative after a reaction time of less than 5 minutes, and no competing attack of the Grignard reagent on the methyl ester function of the substrate **1c** has been observed.^[15] It turned out that the corresponding triflate **1d** (X = OTf) and even the tosylate **1e** (X = OTs) perform equally well, providing product **2** in excellent yields and high reaction rates.

The reaction is virtually independent of the chosen iron salt (Table 2, entries 1–4, 7–9).^[5, 6] The cheap and non-hygroscopic $[\text{Fe}(\text{acac})_3]$ is the most convenient precatalyst from the practical point of view. Only for secondary alkyl Grignard reagents the use of $[\text{Fe}(\text{salen})\text{Cl}]$ is recommended (Table 2, entry 9). The method, however, was found to be highly responsive to the chosen nucleophile. In addition to *n*-alkyl- and *sec*-alkylmagnesium halides with ≥ 2 carbon atoms, which uniformly react without incident, trialkylzincates also constitute suitable reagents (Table 2, entry 16). The use of an organolithium compound, however, failed to afford any cross-coupling product (Table 2, entry 17). We tentatively ascribe

Table 2. Screening of the performance of different iron salts and nucleophiles in cross-coupling reactions with two different aryl chlorides.^[a]

Entry	ArCl	RM	Fe salt [5 %]	ArR [%] ^[b]
1		<i>n</i> -C ₆ H ₁₃ MgBr	$[\text{Fe}(\text{acac})_2]$	90
2		<i>n</i> -C ₆ H ₁₃ MgBr	$[\text{Fe}(\text{acac})_3]$	91
3		<i>n</i> -C ₆ H ₁₃ MgBr	FeCl ₃	88
4		<i>n</i> -C ₆ H ₁₃ MgBr	$[\text{Fe}(\text{salen})\text{Cl}]$	96
5		C ₂ H ₅ MgBr	$[\text{Fe}(\text{acac})_3]$	> 95
6		<i>n</i> -C ₆ H ₁₃ MgBr	$[\text{Fe}(\text{acac})_3]$	> 95
7		<i>n</i> -C ₆ H ₁₃ MgBr	FeCl ₂	> 95
8		<i>n</i> -C ₁₄ H ₂₉ MgBr	$[\text{Fe}(\text{acac})_3]$	> 95
9		<i>i</i> -C ₃ H ₇ MgBr	$[\text{Fe}(\text{salen})\text{Cl}]$	59
10			$[\text{Fe}(\text{acac})_3]$	91 ^[c]
11			$[\text{Fe}(\text{acac})_3]$	88 ^[c]
12			$[\text{Fe}(\text{acac})_3]$	85 ^[c]
13		H ₂ C=CHMgBr	$[\text{Fe}(\text{acac})_3]$	0
14		H ₂ C=CHCH ₂ MgBr	$[\text{Fe}(\text{acac})_3]$	0
15		C ₆ H ₅ MgBr	$[\text{Fe}(\text{acac})_3]$	28
16		Et ₃ ZnMgBr	$[\text{Fe}(\text{acac})_3]$	93
17		<i>n</i> -C ₄ H ₉ Li	$[\text{Fe}(\text{acac})_3]$	0

[a] acac = acetylacetonato, salen = *N,N*-ethylenebis(salicylidenediamidato), MOM = methoxymethyl. [b] GC yields unless stated otherwise. [c] Yield of isolated product.

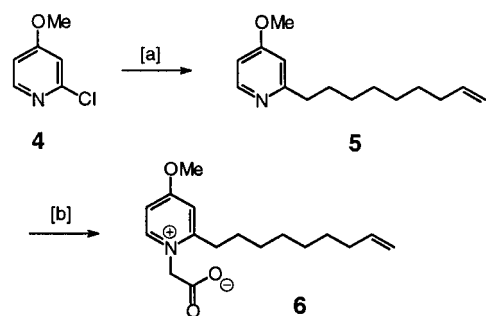
this distinct behavior to the need to form a rather covalent Fe–M (M = Mg, Zn) bond in the active species.^[9, 11, 16] In stark contrast to the successful use of alkylmagnesium halides, all aryl-, allyl- and alkenyl-Grignard reagents investigated invariably led to poor results (Table 2, entries 13–15). This might be caused by a competing catalytic decomposition of such organometallic species in the presence of transition metal salts and aryl halides to form biaryls or dienes, respectively, as documented in a series of classical publications of Kharasch et al.^[17]

With regard to the substrate scope, the iron-catalyzed process turned out to be widely applicable. As can be seen from the results compiled in Table 3, all moderately electron-

Table 3. Yields [%] of iron-catalyzed cross-coupling reactions of alkyl-Grignard reagents with aryl chlorides, triflates, and tosylates.

Nr.	ArX	RMgX	X = Cl	X = OTf	X = OTs
1		<i>n</i> -C ₆ H ₁₃ MgBr	91	87	83
2		<i>n</i> -C ₆ H ₁₃ MgBr	91	80	74
3		<i>n</i> -C ₁₄ H ₂₉ MgBr	94	72	75
4		<i>n</i> -C ₁₄ H ₂₉ MgBr	0	81	0
5		<i>n</i> -C ₆ H ₁₃ MgBr	85 (R = O <i>i</i> Pr)		
6			94 (R = NiPr ₂)		
7		<i>n</i> -C ₁₄ H ₂₉ MgBr	0	90	0
8		<i>n</i> -C ₁₄ H ₂₉ MgBr		81	
9		<i>n</i> -C ₁₄ H ₂₉ MgBr	92	74	82
10		<i>n</i> -C ₁₄ H ₂₉ MgBr	81 (R = H)		
11			95 (R = OMe)		
12		<i>n</i> -C ₁₄ H ₂₉ MgBr	93		
13		<i>n</i> -C ₁₄ H ₂₉ MgBr	41		
14		<i>n</i> -C ₁₄ H ₂₉ MgBr	68		

deficient aryl chlorides and tosylates investigated react with good to excellent yields. In the case of electron-rich arenes, however, the use of aryl triflates is necessary (Table 3, entries 4, 7, 8). In this way a host of different carbo- and heterocyclic products can be prepared. Of particular note among them are the long-chain alkylbenzene sulfonate shown in entry 5 of Table 3, which serves as a precursor for a biologically degradable detergent,^[18] as well as compound **5** (Scheme 4) as the key intermediate of a synthesis of the cytotoxic marine natural product montipyrindine **6**.^[19] The fact that this new method allows the attachment of unsaturated



Scheme 4. Synthesis of the cytotoxic natural product montipyrindine **6**. [a] 8-Nonylmagnesium bromide, [Fe(acac)₃] (5 mol %), THF/NMP, 0 °C → RT, 81 %; [b] 1. BrCH₂COO(*t*Bu), 40 °C; 2. F₃CCOOH, Et₃SiH, CH₂Cl₂, 74 %.

side chains to arene rings (Table 2 and Scheme 4) complements existing methodology for the preparation of substrates suitable for our studies into alkene and alkyne metathesis.^[20, 21]

The assumed mechanistic scenario outlined above is substantiated by the following control experiments. Thus, it has been shown that even highly activated Fe⁰(*) powder^[22] does not readily insert into the C–Cl bond of substrate **1c** even at elevated temperatures. If, however, a suspension of Fe⁰(*) is stirred in the presence of an excess of *n*-C₁₄H₂₉MgCl, the slow dissolution of the solid material with formation of a dark brown to black, homogeneous solution is observed. The latter is able to efficiently catalyze the cross-coupling of added **1c** with the Grignard reagent. This finding is in line with the notion that Fe⁰ centers can be alkylated by organomagnesium compounds and thereby get reduced to Fe species with formally negative oxidation states (e.g. [Fe(MgX)₂])^[10] which likely account for the observed catalytic turnover.^[13] Ongoing studies are aimed at corroborating these mechanistic assumptions, at improving the results in the cross-coupling of arylmagnesium halides with chloroarenes, and at implementing this novel methodology into natural product synthesis.

Experimental Section

A flame-dried two-necked flask was charged under argon with methyl 4-chlorobenzoate (**1c**; 1.00 g, 5.86 mmol), [Fe(acac)₃] (103 mg, 0.29 mmol), THF (35 mL), and NMP (3.3 mL). A solution of *n*-hexylmagnesium bromide (2 M in Et₂O, 3.5 mL, 7.00 mmol) was added by syringe to the resulting red solution, causing an immediate color change to dark brown and finally to violet. The resulting mixture was stirred for 5–10 min, the reaction was diluted with Et₂O and was carefully quenched upon addition of aqueous HCl (1 M, ca. 10 mL). Standard extractive work-up followed by flash chromatography of the crude product (hexanes/ethyl acetate, 30/1) provided compound **2** as a colorless syrup (1.24 g, 91 %). ¹H NMR (300 MHz, CDCl₃): δ = 7.90 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.57 (m, 2H), 1.21–1.29 (m, 6H), 0.84 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 167.1, 148.4, 129.2, 128.7, 51.8, 35.9, 31.2, 31.0, 28.9, 22.5, 13.9; IR: $\tilde{\nu}$ = 1724 cm^{−1}; MS (EI): *m/z* (rel. intensity): 220 (50, [M⁺]), 189 (39), 150 (100), 91 (54), 43 (17).

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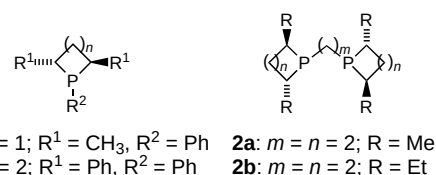
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Mono- and Bidentate Phosphinanes—New Chiral Ligands and Their Application in Catalytic Asymmetric Hydrogenations**

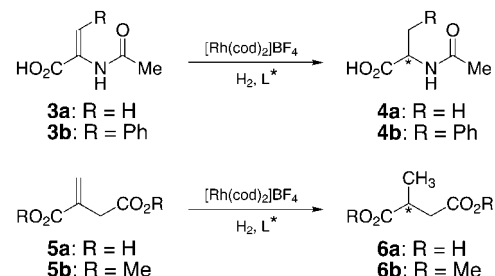
Markus Ostermeier, Jan Prieß, and Günter Helmchen*

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

Chiral phosphanes possessing a modular make-up are important as ligands for asymmetric catalysis with transition metal complexes. The ethylene-bridged BPE ligands **2** and the 1,2-phenylene-bridged DuPHOS ligands,^[1] introduced by Burk et al., and analogues^[2] belong to the most effective ligands and were found to be particularly successful in enantioselective hydrogenations. Even with the monodentate phosphanes **1a** and **1b** enantiomeric excesses of up to 84 and 82 % *ee*, respectively, were achieved in the hydrogenation of



acetamidocinnamic acid (**3a**) (Scheme 1); however, only 12 % *ee* were obtained with **1a** in the case of substrate **5b**.^[3, 4] With the chelate ligands **2a** and **2b** hydrogenations of methyl 2-acetamidoacrylate furnished 91 and 98 % *ee*, respectively.^[1b]



Scheme 1. Asymmetric catalytic hydrogenations. cod = cycloocta-1,5-diene, L* = chiral ligand.

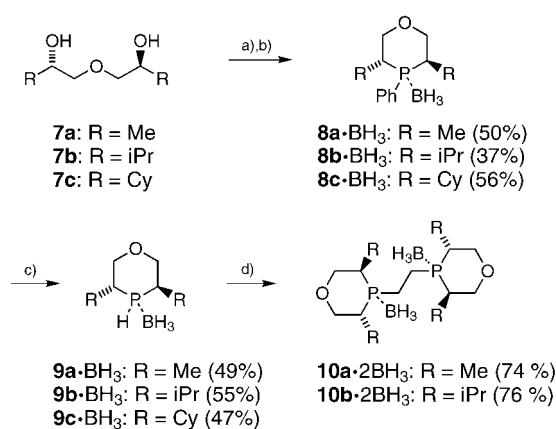
Upon inspection of the literature it was observed that phosphetanes^[5] (**1**, *n* = 1) and phospholanes^[1–4] (**1**, *n* = 2) had been studied intensively and phosphiranes^[6] marginally, surprisingly however, analogous phosphinanes (**1**, *n* = 3) were found to be unknown. Since there is a marked influence of ring size on the properties of ligands, we decided to fill this void in the arsenal of ligands. We now report the first ligands

[*] Prof. Dr. G. Helmchen, Dipl.-Chem. M. Ostermeier, Dr. J. Prieß
Organisch-chemisches Institut, Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
Fax: (+49) 6221-54-4205
E-mail: G.Helmchen@urz.uni-heidelberg.de

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of this type and their use in asymmetric hydrogenation. In the course of these studies another void in the arsenal of ligands was discovered, namely the fact that so far only tertiary phosphanes were employed as P ligands in asymmetric hydrogenation. We were able to fill this void too and now report the first, to the best of our knowledge, asymmetric hydrogenations with secondary phosphanes.

To provide a system with a modular make-up, an additional heteroatom was incorporated into the phosphinane ring (Scheme 2). The syntheses started with the diol ethers **7**; these were obtained by known procedures involving deamination of amino acids to give hydroxy acids, reduction of these to diols, and subsequent Williamson synthesis.^[7] Reaction of the mesylates of the diol ethers **7** with dilithiophenylphosphane^[1a] furnished the oxaphosphinanes **8**; because of their sensitivity against oxygen, these were transformed with BH₃·THF to the storable protected phosphanes **8**·BH₃.^[8]



Scheme 2. Synthesis of the ligands **8**–**10**. a) MsCl (2.5 equiv), NEt₃ (3.5 equiv), DMAP (0.25 equiv), CH₂Cl₂, 0 °C, 2 h; b) 1. H₂PPh (1 equiv), *n*BuLi (2.1 equiv), THF, –78 °C, 30 min, then mesylate, THF, –78 °C → RT, 16 h, 2. BH₃·THF, –78 °C → 20 °C, 12 h; c) 1. Li (4 equiv), THF, 20 °C, 6 h, 2. MeOH, 20 °C, 10 min; d) *n*BuLi (1.05 equiv), THF, –78 °C, 30 min, then TsOCH₂CH₂OTs (0.475 equiv), –78 °C → 20 °C, 48 h.

Rhodium-catalyzed asymmetric hydrogenations were initially carried out with acetamidocinnamic acid (**3b**) and itaconic acid (**5a**) as typical substrates (Scheme 1). The precatalysts were prepared by reaction of the oxaphosphinanes, obtained after removal of the protective BH₃ group, with [Rh(cod)₂]BF₄ in THF (molar ratio ligand:Rh = 2.2:1). Conditions used for the hydrogenations are given in Table 1.

In view of recent successes with monodentate ligands,^[9] the oxaphosphinane **8b** was initially tested. This gave rise to slow reactions and enantiomeric excesses (Table 1, entries 1 and 2) were lower than those obtained with analogous monodentate phospholanes^[4] and phosphetanes.^[3] Seemingly, the steric bulk of the ligands prevented an arrangement in the catalyst complex favorable for hydrogenation. Therefore, the phenyl group at the phosphorus center was replaced by hydrogen. This was achieved by reaction of the borane adducts **8**·BH₃ with lithium (4 equiv) in THF to give borane adducts **9**·BH₃ (Scheme 2).^[10] For the formation of the precatalyst, the borane adduct was heated with 1.2 equivalents of 1,4-diazabicyclo[2.2.2]octane (DABCO) in THF for 2 h at reflux and

Table 1. Enantioselective Rh-catalyzed hydrogenations.^[a]

Entry	Ligand	Substrate	Solvent	Rh: Substrate	ee [%] (Config.)
1 ^[c]	8b	3b	MeOH	1:100	46.5 (S)
2	8b	5a	MeOH	1:100	72.9 (R)
3	9b	3b	MeOH	1:100	86.0 (S)
4 ^[b]	9b	3a	<i>i</i> PrOH	1:100	80.0 (S)
5	9b	5a	<i>i</i> PrOH	1:100	92.1 (R)
6	9b	5a	<i>i</i> PrOH	1:500	92.6 (R)
7	<i>ent</i> - 9c	3a	<i>i</i> PrOH	1:100	92.2 (R)
8	<i>ent</i> - 9c	3b	CH ₂ Cl ₂	1:100	90.0 (R)
9	<i>ent</i> - 9c	5a	<i>i</i> PrOH	1:100	96.0 (S)
10	<i>ent</i> - 9c	5a	<i>i</i> PrOH	1:500	95.5 (S)
11	10a	3a	MeOH	1:100	97.5 (R)
12	10a	3a	MeOH	1:1000	97.4 (R)
13	10a	3b	MeOH	1:100	94.6 (R)
14	10a	3b	MeOH	1:1000	94.2 (R)
15	10a	5a	<i>i</i> PrOH	1:100	94.2 (S)

[a] Reaction conditions: 1.1 bar of H₂; 20 °C; 24 h; c(substrate) = 0.1 mol L^{–1}; molar ratio ligand:Rh = 2.2:1, catalyst preparation see text. For ligand **10a** the molar ratio **10a**:Rh = 1.1:1 was used. In every case complete conversion was achieved. For determinations of enantiomeric purities the crude reaction products were transformed into the methyl esters and these were analyzed by GC; column Chrompack-CP-Chiralsil-L-Val (25 m × 0.25 mm), flow: 100 mL h^{–1}, 105 °C: *t*_R[(R)-**4a**-Me] = 4.3 min, *t*_R[(S)-**4a**-Me] = 5.0 min; 150 °C: *t*_R[(R)-**4b**-Me] = 11.3 min, *t*_R[(S)-**4b**-Me] = 12.3 min; column: Chrompack-CP-γ-Cyclodextrin-TA (30 m × 0.25 mm), flow: 60 mL h^{–1}, 70 °C: *t*_R[(S)-**6b**] = 22.8 min, *t*_R[(R)-**6b**] = 25.6 min. Absolute configurations were determined by comparison with known signs of optical rotations: a) R. D. Larsen, R. A. Reamer, E. G. Corley, P. Davis, E. J. J. Grabowski, P. J. Reider, I. Shinkai, *J. Org. Chem.* **1991**, 56, 6034–6038; b) R. Eck, H. Simon, *Tetrahedron* **1994**, 50, 13631–13640; c) H. Takahashi, K. Achiwa, *Chem. Lett.* **1989**, 305–308. [b] Reaction temperature: 5 °C. [c] Conversion: 15 %.

the resultant solution was added to a cooled (–78 °C) solution of [Rh(cod)₂]BF₄ in CH₂Cl₂. NMR spectroscopic analysis showed that, independent of the amount of ligand, only precatalyst complexes with two coordinated ligands were formed.^[11]

In all cases, enantioselectivities of the hydrogenations were higher and the reactions faster^[12] with the ligands **9** (Table 1, entries 3–10) than with the P-phenyl ligands **8**. Using ligand **9b**, we obtained 92.6 % ee for the hydrogenation of itaconic acid (**5a**) after optimization of the solvent (Table 1, entry 6). The catalyst system is very robust against acidic (AcOH) or basic (NEt₃) additives, which did not significantly influence the level of enantioselectivity. With substrate/catalyst ratios of 100:1 and 500:1 turnover frequencies of 91 and 313 h^{–1}, respectively, were obtained. In the case of itaconic acid the enantiomeric excess was increased to 96.0 % ee with the more bulky ligand *ent*-**9c** (Table 1, entries 7–10).

So far we could not obtain crystals of a Rh^I complex suitable for X-ray crystallography; however, we were successful with an analogous platinum complex [PtCl₂(**9b**)₂] (Figure 1).^[13] Oxaphosphinane rings display the chair conformation and are arranged in such a way that the axial P–H bonds are in juxtaposition. Because of the relative rotational state of the rings, a simple sector model for an analogous Rh complex with classification of substituents according to their steric effects cannot be established at present.

For the preparation of the bidentate chelate ligands the oxaphosphinanes **9**·BH₃ were deprotonated with *n*BuLi and the resultant phosphides were allowed to react with 1,2-

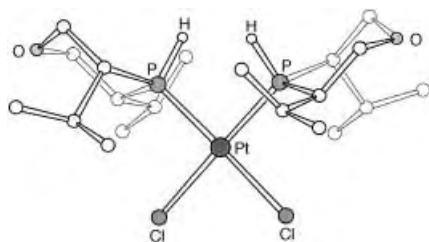
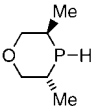
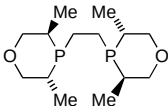
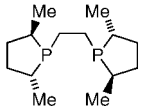


Figure 1. Structure of the complex $[\text{PtCl}_2(\mathbf{9b})_2]$ in the crystal.

ditosyloxyethane to give the crystalline ligands $\mathbf{10} \cdot 2\text{BH}_3$. Attempted decomplexation with DABCO was not successful, good results were obtained with a method developed by Livinghouse et al. (1. $\text{HBF}_4 \cdot \text{Et}_2\text{O}$, 2. K_2CO_3).^[14] The hydrogenations were carried out using a molar ratio ligand:Rh = 1.1:1 (Table 1, entries 11–15). Enantioselectivities were distinctly higher with ligand **10a** than with ligand **2a**.^[15] However, the more bulky ligand **10b** induced lower levels of enantiomeric excess and conversion. Generally, bulky substituents R (Scheme 2) were found to be favorable for monodentate oxaphosphanes **9** but unsuited for chelate ligands **10**.

The configurational relationships for hydrogenations with the various ligands are summarized in Table 2. As found for most monodentate ligands,^[9] a simple rationale is so far not apparent. The inverse configurations of product **6b** induced by ligands **10a** and **2a** in the case of substrate **5b** demonstrate that analogous five- and six-membered-ring systems differ considerably.

Table 2. Configurational relationships between hydrogenation products and the ligands **9a**, **10a**, and **2a**.

Products	Configuration of the hydrogenation products with ligand		
			
	9a	10a	2a
4a	S	R	R ^[a]
4b	S	R	R ^[a]
6a	R	S	—
6b	S	S	R

[a] In the case of ligand **2a** Burk et al. have used the corresponding methyl esters as substrates.

In conclusion, the results described above demonstrate that six-membered-ring phosphanes are promising new ligands. Oxaphosphanes, whose modular make-up allows numerous variations, give rise to high degrees of enantioselectivity in asymmetric hydrogenations as secondary monodentate P ligands and also when they are combined into chelate ligands. It is expected that the new ligands will be applied in other catalyzed reactions.

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- [12] Here too, a reaction time of 24 h was chosen, although hydrogenations were completed sooner.
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DNA On Silicon Devices: On-Chip Synthesis, Hybridization, and Charge Transfer**

Andrew R. Pike, Lars H. Lie, Robert A. Eagling, Lyndsey C. Ryder, Samson N. Patole, Bernard A. Connolly, Benjamin R. Horrocks, and Andrew Houlton*

Surface-immobilized DNA has an increasing number of roles in science and technology because of the ease with which it can be manipulated chemically and enzymatically in a highly controlled manner. Complex DNA architectures^[1] and the use of DNA as a scaffold for making electronic connections^[2] have been reported, and the use of DNA as a component in so-called molecular electronics has been frequently advocated.^[3] Applications also include DNA microarrays^[4] for sequencing through hybridization, the study of gene expression, and even for prototype computing devices which utilize the fidelity of the hybridization reaction.^[5–7] In most cases, the DNA is immobilized on glass, oxidized silicon wafers, or other insulating supports. Methods for combining DNA with electronic materials are anticipated to be increasingly important in light of the considerable interest in DNA-based nanotechnology,^[1] DNA-mediated charge transfer,^[8] and DNA-based wires.^[2] For substrates such as gold^[9] or Si,^[10] where there is the possibility of charge transfer through the DNA to the surface, immobilization has relied upon the attachment of presynthesized strands. However, to date there has been no demonstration of the use of automated solid-phase DNA synthesis nor charge transfer through DNA-based assemblies at a semiconductor. For many proposed applications the ability to combine microelectronic processing techniques,^[11] for example, photolithography and micromachining, with automated chemical synthesis has clear advantages. Herein we outline a method that enables the straightforward integration of DNA technology with microelectronics.

Hydrogen-terminated surfaces represent the initial state from which silicon semiconductor devices are fabricated.^[11] Chidsey and co-workers first demonstrated that such single-crystal surfaces^[12] react with alkenes to give chemically robust Si–C-bonded monolayers, and further advances have shown the applicability of this chemistry to porous silicon.^[13–15] The reaction may be driven by thermal, catalytic, electrochemical, and photochemical methods,^[13, 16] and patterning of the monolayers, for example, by using photolithographic techniques, is possible. We have used a simple protecting group method to produce monolayers with terminal OH groups

(Figure 1); hydrogen-terminated silicon surfaces of oriented (111) single-crystal and porous silicon were alkylated with 4,4'-dimethoxytrityl-protected ω -undecenol (trityl = triphenylmethyl) by refluxing it in toluene; this is a previously

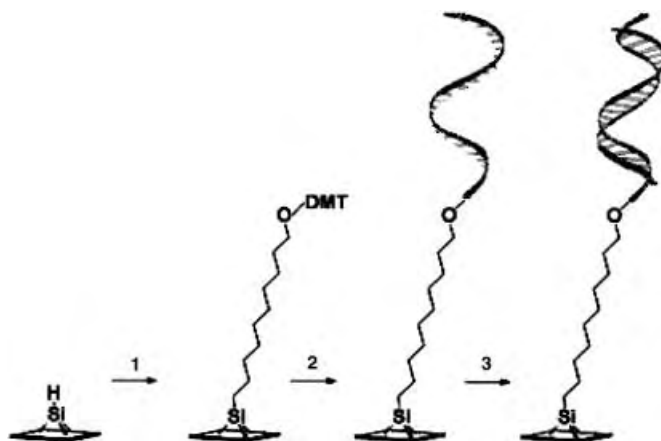


Figure 1. 1) Alkylation of hydrogen-terminated surfaces by reaction with 4,4'-dimethoxytrityl-protected (DMT) ω -undecenol in refluxing toluene for 16 h. 2) The alkylated surfaces were loaded onto a DNA synthesizer followed by deprotection of the on-chip oligonucleotides using anhydrous CH_3NH_2 . 3) Hybridization reaction.

established method to form robust Si–C-bonded monolayers.^[15, 17] The 17-mer oligonucleotides were then synthesized at these modified surfaces with UltraMILD base phosphoramidites (Glen Research, VA, USA) by using a DNA synthesizer and a column assembly modified to accept approximately 1-cm² Si chips. The deprotection step employed anhydrous methylamine^[18] and rinsing with ethyl acetate and water instead of the standard treatment of standing for 12 h in aqueous NH_3 . The surface is not pitted in the course of this treatment, in contrast to methods in which aqueous ammonia is used. In some cases, a cleavable linkage (chemical phosphorylation agent, Glen Research, VA, USA) was inserted at the 3'-terminal position to allow the quality of the oligonucleotide synthesis to be analyzed by gel electrophoresis. Figure 2 compares the electrophoresis data for

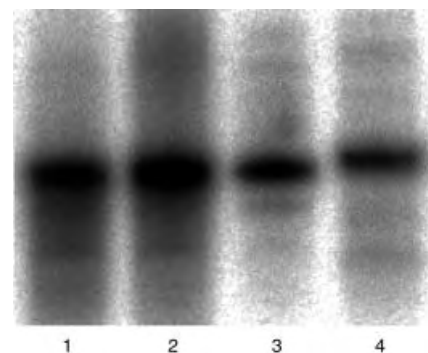


Figure 2. Polyacrylamide gel electrophoresis of oligonucleotides prepared at silicon surfaces. Lanes 1, 2, and 3: 17-mer = 5'-CGGCATCGTACGAT-TAT; 4: 18-mer = ATAATCGTACGATGCCGT. Oligonucleotides were removed from the silicon surfaces (lanes 1 and 2) by incorporating a cleavable linkage (chemical phosphorylation agent) at the 3'-terminus of the strands and so contain a 3'-phosphate group. Lane 1: Si(111) single crystal, lane 2: porous silicon, lanes 3 and 4: 17- and 18-mers from a commercial control-pore glass support (CPG).

[*] Dr. A. Houlton, A. R. Pike, L. H. Lie, R. A. Eagling, L. C. Ryder, S. N. Patole, Dr. B. R. Horrocks

Dept of Chemistry

University of Newcastle upon Tyne

Newcastle upon Tyne, NE1 7RU (UK)

Fax: (+44) 191-222-6929

E-mail: andrew.houlton@ncl.ac.uk

Prof. B. A. Connolly

Dept of Biochemistry and Genetics

University of Newcastle upon Tyne

Newcastle upon Tyne, NE1 7RU (UK)

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oligonucleotide strands cleaved from single-crystal, porous silicon and standard silica columns. The quality of synthesis at the silicon surfaces is comparable to that obtained at commercial silica supports.

Silicon-bound 17-mer strands (5'-CGGCATCGTACGAT-TAT-3') act as substrates for T4 polynucleotide kinase as shown by radiolabeling using [γ - ^{32}P]adenosine-5'-triphosphate ([γ - ^{32}P]ATP). Phosphorimaging was also used to confirm that the Si-DNA oligonucleotides undergo hybridization with complementary strands. Hybridization was directed to specific regions of DNA-patterned porous silicon (Figure 3), fabricated using a combination of photolithography and anodic etching. Figure 3 compares the mask and DNA-patterned wafer with the phosphorimage after hybridization. No discernible image is observed for controls where the surfaces are exposed to ^{32}P -labeled oligonucleotides with the same sequence as present on the surface.



Figure 3. A DNA-patterned Si surface was formed by a combination of photolithography and anodic etching to form porous silicon regions. The surface was functionalized with a 17-mer oligonucleotide (sequence 1) according to the scheme. Left: the mask, center: Si wafer after on-chip DNA synthesis, and right: a phosphorimage after hybridization with a complementary ^{32}P -labeled oligonucleotide. The center picture shows the porous silicon pattern which corresponds with the dark regions of ds-DNA (right).

A mechanism for charge transfer between the DNA and the silicon must be provided in order to combine DNA with microelectronics. Previous workers have shown that DNA can be used as a scaffold at which to plate silver to make metallic connections.^[2] Alternatively, the charge-transfer properties of DNA itself^[8] can be employed with enhancement by non-covalent binding of redox-active molecules, such as intercalators. The binding of methylene blue^[9c] to the Si-DNA duplex structures allowed electron transfer to be observed. Cyclic voltammograms exhibited a reversible wave characteristic of a surface-bound redox process (Figure 4). Silicon crystals bearing only single-stranded DNA (ss-DNA) showed no electrochemical response after exposure to the intercalator, which indicated the need to assemble double-stranded DNA (ds-DNA) to effect binding of the redox-active agent.

The surface coverage of methylene blue was found by integrating the cyclic voltammogram (Figure 4) to be $1.75 \pm 0.3 \times 10^{-12} \text{ mol cm}^{-2}$, and independent of the scan rate over the range 20–200 mV s^{-1} , thus indicating a surface-confined process. A molecular-mechanics model of the Si(111) surface with ds-DNA attached through the undecenyl linker shows that the double helix is tilted about 30° to the normal and the projection of the attached strand plus linker on the Si(111) face is about 3.5 nm. The corresponding theoretical maximum

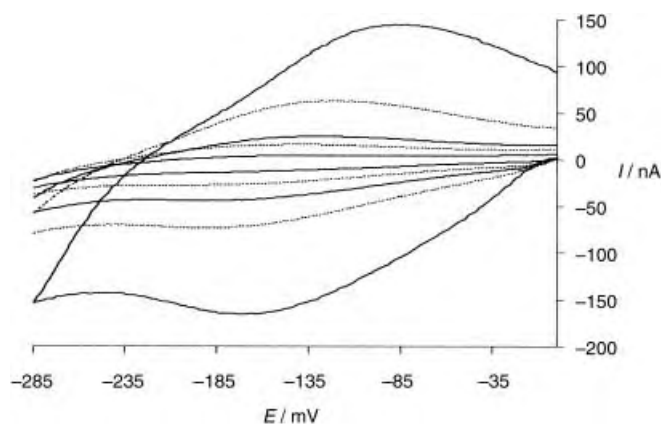


Figure 4. Cyclic voltammogram (HEPES) of methylene blue intercalated into 17-mer duplex strands attached to Si(111) at different scan rates (20–200 mV s^{-1}).

DNA surface coverage is about $2.4 \times 10^{-11} \text{ mol cm}^{-2}$. Hence, these data shows that the double-stranded layer is not close-packed. The surface coverage of ss-DNA was estimated by using $[\text{Ru}(\text{NH}_3)_6]^{3+}$ to be $5.3 \times 10^{-12} \text{ mol cm}^{-2}$.^[19] This is a similar value to that found for thiol-containing oligonucleotides on gold.^[19b]

In summary, while the detailed understanding of its charge-transfer properties continues to be debated, the possibilities for using DNA as a material for the fabrication of nanoscale devices increase. The ability to combine the elegance of solid-phase synthesis with semiconductor electronic materials, such as silicon, may provide yet further scope for development.

Experimental Section

Single-crystal silicon or porous silicon were alkylated with 4,4'-dimethoxytrityl-protected ω -undecanol following published procedures^[14] and used for the oligonucleotides synthesis as described in Figure 1.

Oligonucleotides (32 μL in buffer) were radioactively labeled at the 5'-ends using [γ - ^{32}P]ATP and T4 polynucleotide kinase.^[20] Salt and excess [γ - ^{32}P]ATP were removed with a QIAquick nucleotide removal kit (Qiagen). The samples were immersed in denaturing buffer (formamide containing 1 mg mL^{-1} each of bromophenol blue and xylene cyanol, 0.5 M ethylenediaminetetraacetate (EDTA), 8 M urea). Electrophoresis on polyacrylamide denaturing gels (12%) containing 8 M urea were run in tris-borate ethylenediamine tetraacetic acid (TBE) buffer (89 mmol tris(hydroxymethyl)aminoethane (Tris) borate (pH 8.2), 1 mmol EDTA at 35 W for 30 mins).

Hybridization reaction conditions involved applying the oligonucleotide solution (15 mmol oligonucleotide, 2-[4-(2-hydroxyethyl)-1-piperazinyl]-ethanesulfonic acid (HEPES) buffer pH 7.5, 200 mM NaCl, 1 mM EDTA) to the DNA-modified Si chips for 10 min. The chips were then washed with buffer and water. The binding of methylene blue involved immersion of the chips in HEPES buffer at pH 7.5 containing 0.1 mM intercalator followed by exhaustive washing with buffer.

Patterned porous silicon was prepared using a modification of the procedure described by Ronkel and Schultze.^[21] The 17-mer oligonucleotide (sequence 1) was then attached as described.

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A Diferric Peroxo Complex with an Unprecedented Spin Configuration: An $S = 2$ System Arising from an $S = 5/2$, $1/2$ Pair**

Helga Hummel, Yasmina Mekmouche, Carole Duboc-Toia, Raymond Y. N. Ho, Lawrence Que, Jr., Volker Schünemann, Fabrice Thomas, Alfred X. Trautwein, Colette Lebrun, Marc Fontecave,* and Stéphane Ménage*

Dioxygen binding and activation are important biological steps in the mechanisms of a number of metalloproteins. For metalloenzymes containing non-heme diiron active sites,^[1] such as methane monooxygenase, a diferric peroxo species is a key intermediate in the enzymatic mechanism.^[2] To date, the binding modes of the peroxide at these active centers remain to be fully established and more chemical models are required. So far, three coordination modes of this anion have been determined in iron coordination chemistry, namely μ -1,2-peroxo,^[3] η^1 -hydroperoxo,^[4] and η^2 -peroxo modes.^[5] We recently showed that the (μ -oxo)-diferric complex $[\text{Fe}_2\text{O}(\text{pb})_4(\text{H}_2\text{O})_2](\text{ClO}_4)_4$ (**1**- $(\text{ClO}_4)_4$) with the (–)4,5-pinene derivative pb as ligand reacted with H_2O_2 to afford a mixture of two peroxo adducts, as indicated by resonance Raman spectroscopy.^[6] Here, we demonstrate with new spectroscopic studies that one is a μ -1,2-peroxo adduct (**2**) and the other is a μ -oxo-diferric complex in which the peroxide binds in a monodentate fashion to one iron center (**3**; Scheme 1). This new structural motif engenders an unprecedented ground spin state ($S = 2$) derived from the coupling of an $S = 5/2$ and an $S = 1/2$ ion in the diferric unit.

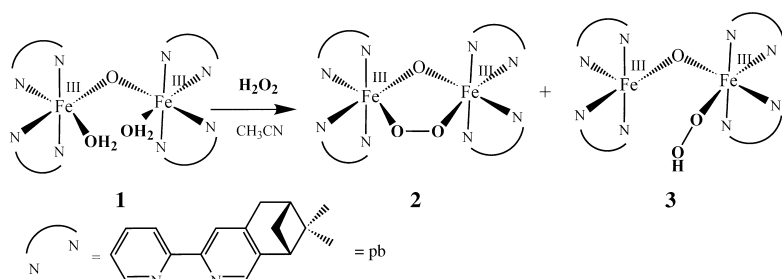
The addition of 50 equivalents of H_2O_2 to 1 mM complex **1** in acetonitrile at -40°C caused the appearance of an intense, broad charge-transfer band at 680 nm ($\epsilon = 2000 \text{ M}^{-1} \text{ cm}^{-1}$,

- [*] Prof. M. Fontecave, Dr. S. Ménage, Dr. H. Hummel, Dr. Y. Mekmouche
Laboratoire de Chimie et Biochimie des Centres Rédox Biologiques
UMR Université Joseph Fourier/CNR/CEA 5047
DBMS/CB
17 rue des Martyrs, 38054 Grenoble Cédex 9 (France)
Fax: (+33)4-38 78 91 24
E-mail: mfontecave@cea.fr, smenage@cea.fr
- Dr. C. Duboc-Toia
Laboratoire des Champs Magnétiques Intenses de Grenoble
Max-Planck Institut, Grenoble (France)
- Dr. R. Y. N. Ho, Prof. L. Que, Jr.
Department of Chemistry and Center for Metals in Biocatalysis
University of Minnesota, Minneapolis, MN 55455 (USA)
- Dr. V. Schünemann, Dr. F. Thomas, Prof. A. X. Trautwein
Institut für Physik der Medizinischen Universität
Ratzeburger Allee 160, 23538 Lübeck (Germany)
- C. Lebrun
Service de Chimie Inorganique et Biologique, DRFMC CEA-Grenoble (France)

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author. S1: ESI-MS spectrum and characteristic fragments of **1** + H_2O_2 solution; S2: Mössbauer spectrum of the mixture recorded at 20 mT.



Scheme 1. Products of the reaction between **1** and H_2O_2 .

based on a dinuclear unit) in the UV/Vis spectrum. The presence of two pairs of vibrations in the resonance Raman spectrum of the deep green solution indicated the presence of two different peroxo species.^[3–5] Excitation profile studies showed that the 867 and 491 cm^{-1} features in the Raman spectrum are associated with one chromophore, named complex **2**, that is red shifted relative to a second chromophore, complex **3**, associated with the 806 and 618 cm^{-1} features.^[6] Furthermore, the shift of -44 and -48 cm^{-1} for the features at 806 and 867 cm^{-1} , respectively, observed with $\text{H}_2^{18}\text{O}_2$ is consistent with O–O vibrations for distinct iron peroxo species. The 867 and 491 cm^{-1} pair of vibrations of complex **2** closely matches those associated with (μ -1,2-peroxy)diiron(III) complexes,^[3] while the 806 and 618 cm^{-1} features of complex **3** correspond to the Raman features of mononuclear low-spin Fe^{III} -OOH species.^[4] The appearance of the latter prompted us to confirm the presence of a low-spin Fe^{III} -OOH species by X-band EPR spectroscopy.^[4] However, the solution displayed only minor amounts of EPR active high-spin and low-spin ferric species (less than 5 % total).

A Mössbauer study was then initiated to shed more light on this apparently contradictory situation. A 4.2 K Mössbauer spectrum was obtained for a sample derived from the reaction of ^{57}Fe -labeled complex **1** with H_2O_2 , and revealed the presence of several different iron species.^[7] The 20 mT spectrum could be fitted with four quadrupole doublets (see Supporting Information). That all four components were quadrupole doublets indicated that most of the Fe ions in the sample were not slowly relaxing half-integer spin ions, which would give rise to a six-line pattern at 4.2 K in such small applied fields (20 mT). The latter situation has been observed in activated bleomycin^[8] and a mononuclear low-spin ferric η^1 -hydroperoxo species $\text{Fe}(\text{pb})_2\text{-OOH}$, recently characterized.^[9] The absence of a prominent six-line pattern, even at 0.17 T (Figure 1a), is thus consistent with the absence of intense EPR signals from half-integer spin species.^[10] One doublet, denoted as (A) in Figure 1a has parameters that correspond to the initial diferric complex **1** ($\delta_1 = 0.48$ mm s^{-1} , $\Delta E_{\text{O}_1} = 1.53$ mm s^{-1} , 38 %). Two other doublets, (B) and (C) ($\delta_2 = 0.49$ mm s^{-1} , $\Delta E_{\text{O}_2} = 0.62$ mm s^{-1} , 36 % and $\delta_3 = 0.43$ mm s^{-1} , $\Delta E_{\text{O}_3} = 0.49$ mm s^{-1} , 13 %), correspond to two new species with parameters typical for high-spin Fe^{III} centers. The fourth doublet (D) can be fitted with parameters typical

of a low-spin Fe^{III} center ($\delta_4 = 0.23$ mm s^{-1} , $\Delta E_{\text{O}_4} = 1.64$ mm s^{-1} , 13 %). The only way to rationalize the presence of a low-spin Fe^{III} component in the Mössbauer spectrum without a corresponding X-band EPR signal is to couple it with another half-integer spin ion to form an integer spin species. The presence of a high-spin iron component in the exact percentage as the low-spin iron center (both 13 %) suggests that these two components could be exchange-coupled to afford an effective $S = 2$ or $S = 3$ species.

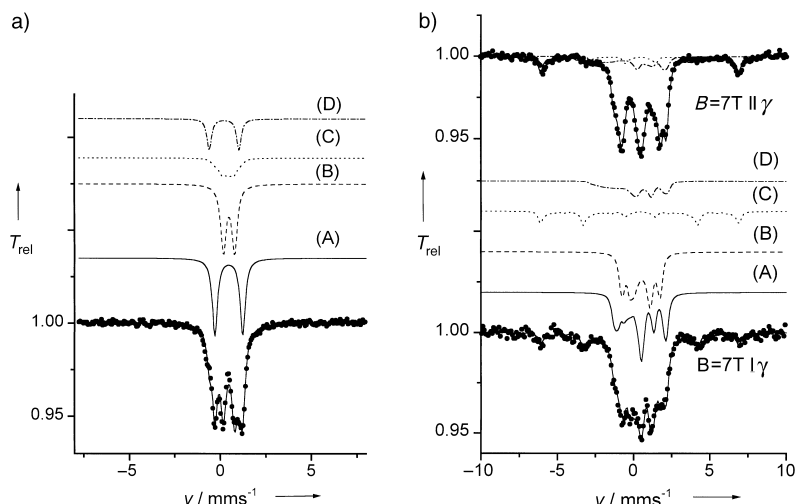


Figure 1. Mössbauer spectra of ^{57}Fe -labeled complex **1** with 50 equivalents H_2O_2 in acetonitrile. a) 0.17 T; b) 7 T (γ -rays perpendicular to the applied magnetic field); (—) Fe_A ; (---) Fe_B ; (····) Fe_C ; (· · · ·) Fe_D (for parameters, see Table 1).

In fact, signals for such an integer spin system were observed with the use of high-frequency EPR spectroscopy (HF-EPR). A temperature-dependent study could not be carried out because all the signals disappeared above 5 K. In all cases the spectra were incomplete, a result of the large zero-field splitting of the system and of the fact that all the observed transitions are forbidden ($\Delta m_s > 1$). However, thanks to a multifrequency analysis (190–345 GHz), the data shown in Figure 2 could be simulated using a full-matrix

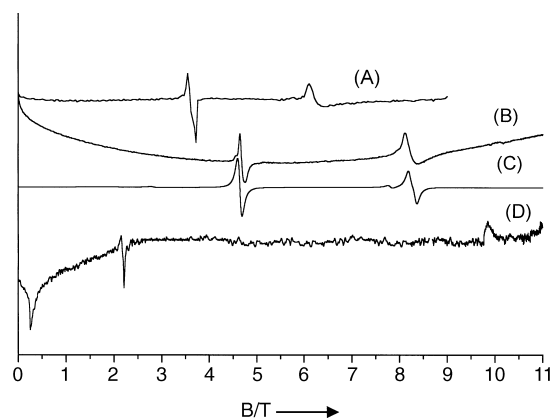


Figure 2. Experimental (A, B, and D) and simulated (C) HF-EPR spectra of 5 mm **1** + 50 equivalents of H_2O_2 in acetonitrile measured at 230 GHz (A), 285 (B and C), and 345 GHz (D) at 5 K; the parameters used for the simulation are reported in the main text.

diagonalization procedure for Equation (1), where $\mathbf{B}$ = magnetic field, $\mathbf{g}$ = electronic g tensor, D = zero-field splitting, E/D = rhombicity parameter.^[11] Fitting parameters acceptable for all frequencies were found only by taking into account an $S=2$ ground state in the limit of strong exchange.^[12] This $S=2$ system is axial ($E/D=0$) with $D = (-4.15 \pm 0.05) \text{ cm}^{-1}$, $g_{\parallel} = 1.97 \pm 0.005$, and $g_{\perp} = 2.00 \pm 0.005$.

$$\mathcal{H} = \beta \mathbf{B} \mathbf{g} \mathbf{S} + D[\mathbf{S}_z^2 - 1/3 \mathbf{S}(\mathbf{S}+1) + E/D(\mathbf{S}_x^2 - \mathbf{S}_y^2)] \quad (1)$$

The $S=2$ assignment has been confirmed by high-field Mössbauer spectroscopy (Figure 1b). This analysis confirmed that doublets (A) and (B) have $S=0$ ground states, which correspond to complexes **1** and **2**, respectively.^[6,8] Different behavior was found for the remaining two components (C) and (D) which represent 26% of the total iron, and were assigned to the proposed coupled $S=5/2$, $1/2$ pair of complex **3**. Using the fine structure parameters derived from the HF-EPR fitting (see above), we have applied the spin projection technique to determine the magnetic hyperfine coupling tensor $\mathbf{A}$ of complex **3** which determines its magnetic splitting in the Mössbauer spectrum.^[12] Assuming that the electronic ground state of the spin-coupled $S=1/2$ site is similar to that of the low-spin hydroperoxo species $(\text{pb})_2\text{Fe}^{\text{III}}\text{-OOH}$ characterized previously,^[9] we have used $\mathbf{A}_{\text{local}}/\mu_N g_N = (-40, -8, +5) \text{ T}$ for the $S=1/2$ site in our analysis of the spin Hamiltonian.^[8] To reproduce the magnetic Mössbauer spectra shown in Figure 1 we get for the $S=5/2$ site $\mathbf{A}_{\text{local}}/\mu_N g_N = -20.1 \text{ T}$, a value which is usually observed for five-coordinate ferric high-spin centers.^[13] Therefore, we consider it as very likely that the ferric high-spin site of complex **3** is five coordinate. The $\mathbf{A}$ tensors of the coupled $S=2$ spin system given in Table 1 are calculated by means of $\mathbf{A} = C\mathbf{A}_{\text{local}}$, where $\mathbf{A}_{\text{local}}$ is the $\mathbf{A}$ tensor of the individual paramagnetic site. The value of C is obtained from ref. [12] ($7/6$ for $S=5/2$ and $-1/6$ for $S=1/2$ sites). Taken together, HF-EPR and Mössbauer data definitively define complex **3** as an $S=2$ system derived from the antiferromagnetic coupling of an Fe^{III} ($S=1/2$) ion and an Fe^{III} ($S=5/2$) ion, perhaps mediated by the μ -oxo bridge. Spin projection afforded the spin-Hamiltonian parameters for the high-spin iron(III) center, in particular the D value: $D_{(S=5/2)} = -3.11 \text{ cm}^{-1}$,^[12] the highest value observed thus far for high-spin non-heme ferric systems.^[14]

The formulations for **2** and **3** (Scheme 1) have been further confirmed by electrospray mass spectrometry.^[15] We detected two new intense ESI-MS peaks at m/z 580.4 (80%) and 630.2 (50%), which can be attributed to the $[\text{Fe}_2(\text{pb})_4\text{O}(\text{OO})]^{2+}$ and $[\text{Fe}_2(\text{pb})_4\text{O}(\text{OOH})(\text{ClO}_4)]^{2+}$ ions, associated to **2** and **3**, respectively. The observed isotopic distribution patterns of these two peaks matched the calculated isotopic distributions (see the Supporting Information).

In conclusion, we have demonstrated that the reaction of **1** with hydrogen peroxide generated two (μ -oxo)diferric peroxo adducts, differentiated by the coordination mode and the protonation state of the peroxide ligand (Scheme 1). Although a μ -oxo- μ -peroxo complex similar to **2** has been observed,^[16] to our knowledge complex **3** is the first example of a diferric coupled system in which the two local spin configurations are different. This particular electronic structure certainly results from the binding of the hydroperoxide anion to a pyridine-rich Fe^{III} ion which makes it low-spin, as seen previously,^[5] while the other Fe^{III} ion remains high-spin. Complex **3** thus differs from the oxy state of hemerythrin (Hr)^[17] and its recent models,^[18] which display a $S=0$ ground state $\text{Fe}(\text{OOH})\text{-O-Fe}$ site with two coupled $S=5/2$ ferric ions. Finally, complex **3** could also be considered as a new possible peroxo intermediate in the catalytic cycle of non-heme iron enzymes.

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Table 1. Mössbauer parameters obtained from the spin-Hamiltonian analysis of the spectra shown in Figure 1.^[a]

Rel. area [%]	S	$D [\text{cm}^{-1}]$	E/D	$\mathbf{g}$	$\delta [\text{mm s}^{-1}]$	$\Delta E_{\text{O}} [\text{mm s}^{-1}]$	$\Gamma [\text{mm s}^{-1}]$	$\eta^{[b]}$	$\beta^{[c]} [^\circ]$	$\mathbf{A}/\mu_N g_N [\text{T}]$
(A) 38	0			–	0.48	–1.53	0.33	0.4	–	–
(B) 36	0			–	0.49	–0.62	0.35	0.7	–	–
(C) 13	2	–4.15	0	2.00, 2.00, 1.97	0.43	0.49	0.28		60	–23.5 –23.5 –23.5
(D) 13	2	–4.15	0	2.00, 2.00, 1.97	0.23	–1.64	0.28	0	90	–6.7 1.3 –0.8

[a] The $\mathbf{g}$ -tensor, the zero-field splitting D , and the rhombicity parameter E/D of components (C) and (D) originating from complex **3** have been taken from the high-field EPR analysis. [b] The asymmetry parameter of the electric field gradient tensor $\mathbf{V}_{ii}$ is given as $\eta = \frac{V_{xx} - V_{yy}}{V_{zz}}$ with $|V_{zz}| \geq |V_{yy}| \geq |V_{xx}|$. [c] Euler angle between the axes system of the $\mathbf{A}$ tensor and of the electric field gradient tensor.

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Thermal Intramolecular Electron Transfer in a Ferrocene–Naphthoquinone Linked Dyad Promoted by Metal Ions**

Shunichi Fukuzumi,* Ken Okamoto, and Hiroshi Imahori*

Electron transfer (ET) in a fixed donor–acceptor distance plays an essential role in photosynthesis, respiration, and redox-mediated enzyme catalysis in biological redox reactions as well as many simple chemical redox reactions.^[1, 2] Thus, ET reactions between donor and acceptor molecules bound to proteins have been studied extensively to understand the factors to control the ET process.^[3] A number of donor–acceptor linked systems with inert rigid spacers have also been developed to study the ET reactions between the donor and acceptor molecules at a fixed distance.^[4–8] In each case, however, photoexcitation of the donor or acceptor moiety or radiolysis is required to start the ET reaction. To date there has been no report on ET in donor–acceptor linked systems started thermally. This situation is taken as a matter of course since it would be impossible to connect donor and acceptor molecules if an ET occurred thermally. However, a number of examples report intermolecular ET reactions with a significant acceleration in the presence of a third component acting as a catalyst or promoter.^[9, 10] Most importantly, thermal intermolecular ET reactions, which would otherwise be unlikely to occur, proceed efficiently in the presence of metal ions which can promote the ET reactions.^[9, 10] In these cases, addition of a metal ion to the donor–acceptor systems can start ET reactions. ET reactions can also be attenuated through noncovalent interactions, such as hydrogen bonding, which plays an important role in biological ET systems.^[11]

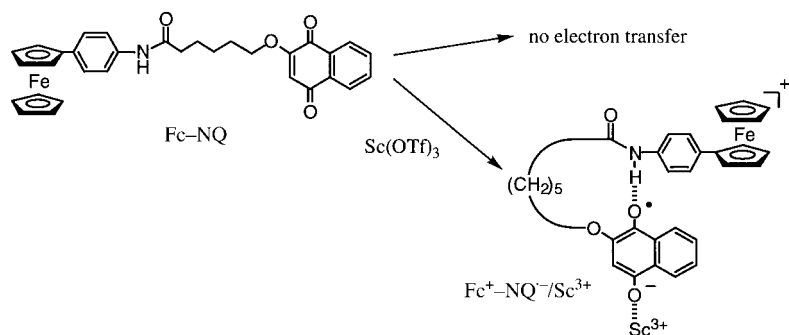
We report herein the first example of an intramolecular ET reaction in a donor–acceptor linked system started thermally by addition of a metal ion. A newly designed ferrocene–naphthoquinone dyad (Fc–NQ) is employed to examine the metal-ion promoted thermal intramolecular ET reaction (Scheme 1).

Details on the synthesis and characterization of Fc–NQ are given as Supporting Information (S1–S3). The cyclic voltammograms of Fc–NQ in acetonitrile (MeCN) exhibited two reversible one-electron redox couples of two redox-active

[*] Prof. S. Fukuzumi, Prof. H. Imahori, K. Okamoto
Department of Material and Life Science
Graduate School of Engineering, Osaka University
CREST, JAPAN Science and Technology Corporation
2-1 Yamada-oka, Suita, Osaka 565-0871 (Japan)
Fax: (+81) 6-6879-7370
E-mail: fukuzumi@chem.eng.osaka-u.ac.jp
imahori@chem.eng.osaka-u.ac.jp

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 Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author. Synthetic procedures of Fc–NQ (S1–S3), the absorption spectrum of Fc–NQ in the Sc³⁺-promoted ET (S4), ESR spectrum of Fc–NQ^{•–} (S5), DFT calculation of Ph–NQ^{•–} (S6), cyclic voltammograms of Fc–NQ in the presence of metal ions (S7) (7 pages, print/PDF).



Scheme 1. OTf = trifluoromethanesulfonate.

moieties at 0.38 V and -0.81 V (versus saturated calomel electrode (SCE)). The former one-electron redox potential corresponds to the Fc^+/Fc couple which agrees with the one-electron oxidation potential of ferrocene (E_{ox}^0 vs SCE = 0.37 V).^[12] The latter potential thereby corresponds to the $\text{NQ}/\text{NQ}^{\cdot-}$ couple. No ET from the Fc to the NQ moiety occurs thermally in Fc–NQ in MeCN at 298 K, as expected from the highly positive free energy change of electron transfer ($\Delta G_{\text{et}}^0 = 1.19$ eV). Addition of 1.0 mM of magnesium perchlorate ($\text{Mg}(\text{ClO}_4)_2$) or lutetium triflate ($\text{Lu}(\text{OTf})_3$) to an MeCN solution of Fc–NQ (2.0×10^{-4} M) resulted in no change in the visible spectrum. However, addition of scandium triflate ($\text{Sc}(\text{OTf})_3$; 1.0 mM) to an MeCN solution of Fc–NQ (2.0×10^{-4} M) resulted in oxidation of the Fc unit as indicated by appearance of the absorption band at 860 nm arising from Fc^+ together with the absorption band at $\lambda_{\text{max}} = 420$ nm (see Supporting Information S4). This data indicates that an intramolecular ET occurs in the presence of Sc^{3+} to produce $\text{Fc}^+-\text{NQ}^{\cdot-}$ in which Sc^{3+} is bound to $\text{NQ}^{\cdot-}$ and that the absorption band at 420 nm is from the $\text{NQ}^{\cdot-}/\text{Sc}^{3+}$ complex (Scheme 1). The absorption band at 420 nm is quite different from that of Fc–NQ $^{\cdot-}$ produced by the chemical reduction of Fc–NQ with naphthalene radical anion ($\lambda_{\text{max}} = 617$ nm) and is clearly a result of complexation with the Sc^{3+} ion.

To confirm formation of the $\text{Fc}^+-\text{NQ}^{\cdot-}/\text{Sc}^{3+}$ ion complex, the ESR spectrum was measured upon addition of $\text{Sc}(\text{OTf})_3$ (20 mM) to an MeCN solution of Fc–NQ (9.1×10^{-3} M). The observed ESR spectrum is shown in Figure 1a together with the computer simulation spectrum (Figure 1b).^[13] The hyperfine coupling constants (hfc) are determined as 1.80 (1H), 1.73 (1H), 0.60 (1H), 0.20 (1H), 0.10 (1H), 0.70 (3H), 0.09 (2H), 0.04 (2H), and 2.57 G (1Sc). The ESR spectrum of Fc–NQ $^{\cdot-}$ produced by the chemical reduction of Fc–NQ with naphthalene radical anion was also measured and the hfc values were determined by the computer simulation (see Supporting Information S5). The hfc values of Fc–NQ $^{\cdot-}$ [2.10 (1H), 1.55 (1H), 0.85 (1H), 0.80 (1H), 0.75 (1H), 0.44 (1H), 0.30 (2H), 0.10 (2H), and 0.05 G (2H)] are somewhat larger than the hfc values of protons of the $\text{Fc}^+-\text{NQ}^{\cdot-}/\text{Sc}^{3+}$ complex. The observed hfc values of Fc–NQ $^{\cdot-}$ can be reproduced by a density functional theory (DFT) calculation with a basis function: double- ζ Slater-type orbital set (frozen core: C (1s), N (1s), O (1s); ADF basis Set II) of Ph–NQ $^{\cdot-}$ in which the Fc moiety is omitted (see Supporting Information S6). The calculation predicts the hfc values of twelve protons in

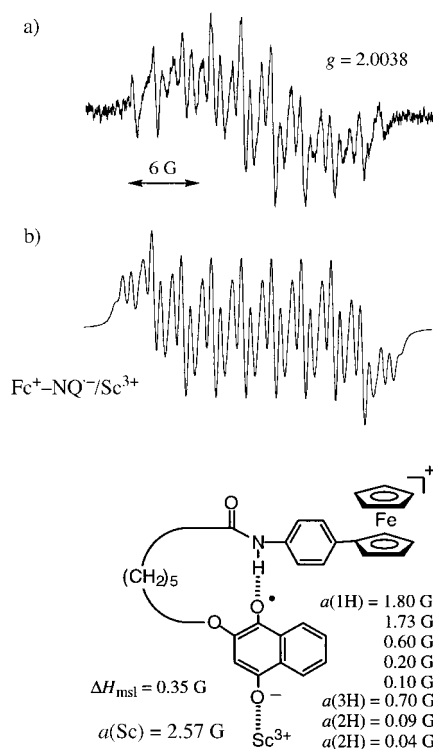


Figure 1. a) ESR spectrum of the $\text{Fc}^+-\text{NQ}^{\cdot-}/\text{Sc}^{3+}$ ion complex (9.1 mM) produced in intramolecular ET of Fc–NQ in the presence of $\text{Sc}(\text{OTf})_3$ (20 mM) in deaerated MeCN at 298 K. b) The computer simulation spectrum.

accordance with the experimental results: 2.38 (1H), 1.32 (1H), 1.01 (1H), 0.76 (2H), 0.41 (1H), 0.30 (2H), 0.10 (2H), and 0.05 G (2H). According to the optimized geometry the O–H distance between the quinone oxygen atom of the $\text{NQ}^{\cdot-}$ moiety and the amide hydrogen is 1.62 Å. This separation indicates hydrogen bond formation between them (S6).^[14] The superhyperfine structure arising from the scandium nucleus ($I = 7/2$) observed in Figure 1a ($a(\text{Sc}) = 2.57$ G) definitely indicates the binding of Sc^{3+} ions to the quinone oxygen atom of the $\text{NQ}^{\cdot-}$ moiety in $\text{Fc}^+-\text{NQ}^{\cdot-}$.^[15] The spin delocalization to the scandium nucleus results in the smaller $a(\text{H})$ values in the $\text{Fc}^+-\text{NQ}^{\cdot-}/\text{Sc}^{3+}$ complex than those in Fc–NQ $^{\cdot-}$. The g value of the $\text{Fc}^+-\text{NQ}^{\cdot-}/\text{Sc}^{3+}$ complex (2.0038) also becomes smaller than the value of Fc–NQ $^{\cdot-}$ ($g = 2.0060$) because of the spin delocalization to scandium nucleus.

The strong binding of Sc^{3+} ions to the quinone oxygen atom of the $\text{NQ}^{\cdot-}$ moiety in $\text{Fc}^+-\text{NQ}^{\cdot-}$ resulted in a remarkable positive shift of the one-electron reduction potential of the NQ moiety (E_{red}^0 versus SCE = 1.21 V), which becomes more positive than the one-electron oxidation potential of the Fc moiety (E_{ox}^0 versus SCE = 0.38 V) as indicated by the cyclic voltammogram of Fc–NQ in the presence of 7.0 mM $\text{Sc}(\text{OTf})_3$ (see Supporting Information S7). A similar but less positive shift of the one-electron reduction potential of the NQ moiety (E_{ox}^0 versus SCE = 0.72 V) was observed in the presence of 7.0 mM $\text{Eu}(\text{OTf})_3$ (S7). In these cases, intramolecular ET from the Fc to the NQ moiety becomes thermodynamically feasible.

Kinetic measurements of thermal intramolecular ET from the Fc to the NQ moiety in Fc–NQ in the presence of Sc^{3+} ion

were performed on a stopped-flow spectrophotometer at 298 K. The rates of appearance of both absorption bands at 800 nm and 420 nm obeyed first-order kinetics and the same first-order rate constants (k_{obs}) were obtained from the first-order plots at both wavelengths. The k_{obs} values determined at 800 and 420 nm increase linearly with increasing Sc^{3+} ion concentration as shown in Figure 2. The first-order dependence of k_{obs} on $[\text{Sc}^{3+}]$ is consistent with the complexation of

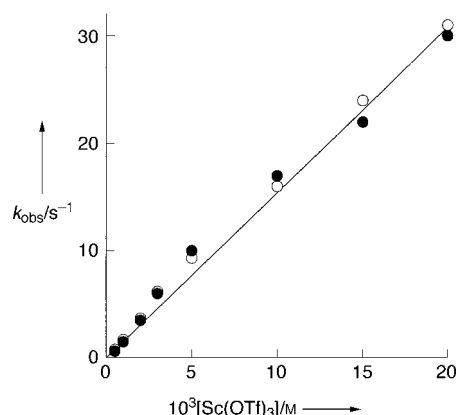


Figure 2. Plot of the rate constant (k_{obs}) determined at 800 nm (●) and 420 nm (○) versus $\text{Sc}(\text{OTf})_3$ concentration for intramolecular ET in Fc-NQ ($2.0 \times 10^{-4} \text{ M}$) in the presence of $\text{Sc}(\text{OTf})_3$ in deaerated MeCN at 298 K.

one Sc^{3+} ion with the $\text{NQ}^{\cdot-}$ moiety in $\text{Fc}^+-\text{NQ}^{\cdot-}$ (Scheme 1).^[16] From the slope of the linear plot of k_{obs} versus $[\text{Sc}^{3+}]$ is obtained the Sc^{3+} -promoted electron transfer rate constant k_{et} as $1.6 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. The promoting effects of other metal ions were also examined and the k_{et} values were determined as 3.3 and $0.3 \text{ M}^{-1} \text{ s}^{-1}$ in the presence of $\text{Y}(\text{OTf})_3$ and $\text{Eu}(\text{OTf})_3$, respectively. This order agrees with the order of Lewis acidity of the metal ions.^[10a]

An intermolecular ET from Fc to 2-methoxy-1,4-naphthoquinone (2-MeONQ) was also examined in the presence of Sc^{3+} ions in MeCN. No ET occurred from Fc to 2-MeONQ in MeCN without Sc^{3+} ions. As is the case of the Sc^{3+} -promoted intramolecular ET in Fc-NQ, an ET from Fc to NQ occurred only in the presence of Sc^{3+} ions to yield Fc^+ and the $\text{NQ}^{\cdot-}/\text{Sc}^{3+}$ complex. The k_{obs} value of the intermolecular ET from Fc ($1.0 \times 10^{-5} \text{ M}$) to 2-MeONQ ($2.0 \times 10^{-4} \text{ M}$) in the presence of 10 mM $\text{Sc}(\text{OTf})_3$ was determined as $5.0 \times 10^{-2} \text{ s}^{-1}$, which is 320 times smaller than the corresponding k_{obs} value of the Fc-NQ intramolecular ET.

In conclusion, the present study has demonstrated for the first time that intramolecular ET in a donor-acceptor linked system can be started thermally by adding an appropriate metal ion which can promote thermal ET which would otherwise be unlikely to occur. This result provides a new way to understand the factors that control thermal ET processes.

Experimental Section

Material: Scandium triflate [$\text{Sc}(\text{OTf})_3$ (99%, F.W. = 492.16)] was obtained from Pacific Metals Co., Ltd. (Taiheiyō Kinzoku). Yttrium triflate [$\text{Y}(\text{OTf})_3$], europium triflate [$\text{Eu}(\text{OTf})_3$], and lutetium triflate [$\text{Lu}(\text{OTf})_3$] were prepared by literature methods.^[17] Magnesium perchlorate

[$\text{Mg}(\text{ClO}_4)_2$] were obtained from Wako Pure Chemical Ind. Ltd., Japan. Chloroform-*d* was obtained from EURI SO-TOP, CEA, France. Thin-layer chromatography (TLC) and flash column chromatography were performed with Art. 5554 DC-Alufolien Kieselgel 60F₂₅₄ (Merck), and Fujisilica BW300, respectively.

Synthesis and General: The synthetic routes toward Fc-NQ and the characterization and general information are described in Supporting Information.

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- [15] The other oxygen atom may form a hydrogen bond with the amide proton as in the case of Fc-NQ^{•-}.
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Evidence for a Hydroxide Ion Catalyzed Pathway in Ester Hydrolysis in Supercritical Water**

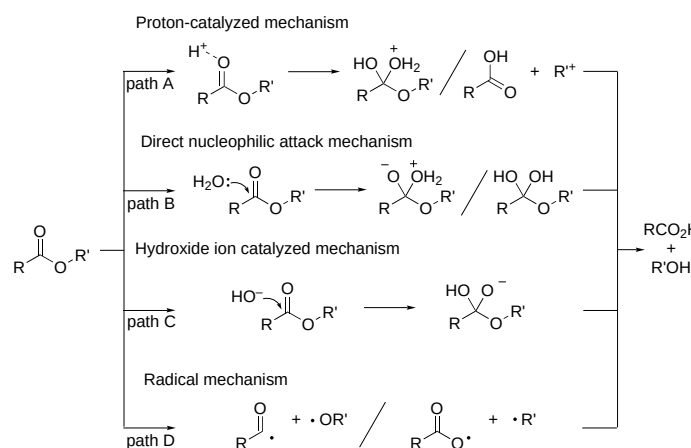
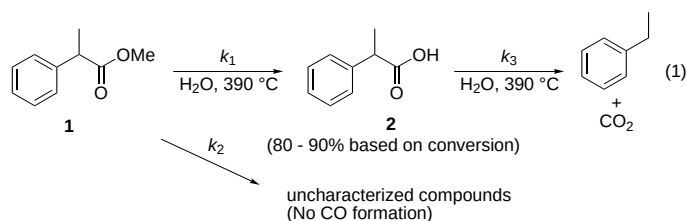
Hiroyuki Oka, Shigeru Yamago,* Junichi Yoshida,* and Okitsugu Kajimoto*

Supercritical water (SCW) has attracted much attention as a novel reaction medium from scientific and technological viewpoints.^[1] It is the most environmentally benign solvent^[2] and possesses high dissolving power for a variety of nonpolar organic compounds because of its weaker hydrogen-bond network^[3] and lower dielectric constant^[4] relative to ambient water. Furthermore, the discovery of the catalytic activity of SCW makes it a promising unique reaction medium for synthetic organic chemistry.^[5, 6]

Among various organic reactions in SCW, hydrolyses of esters and amides are of interest for the decomposition and the recycling of poorly biodegradable synthetic polymers such as poly(ethylene terephthalate).^[7] However, in spite of quite a few reports on practical applications, understanding of the detailed mechanism of this hydrolysis is still quite limited. Although an "autocatalytic" mechanism, in which the carboxylic acid produced by hydrolysis catalyzes the reaction (Scheme 1, path A), was proposed by analogy with the mechanism of nitrile hydrolysis,^[1b, 8] no detailed mechanistic studies have been performed until recently. A mechanistic

study in sub- and supercritical water revealed that the rate of hydrolysis decreases significantly near the critical point,^[9] and the results were explained by a change in mechanism from acid-catalyzed reaction in subcritical water to direct nucleophilic attack of water in SCW (path B). Since the dissociation constants of carboxylic acids decrease considerably in SCW,^[10] a negligible effect of the acid generated by hydrolysis seems reasonable, although the validity of the proposed mechanism has remained unclear.^[11] We were intrigued by the possible involvement of hydroxide ions dissociated from SCW (path C), because base-catalyzed hydrolysis proceeds much faster than the acid-catalyzed reaction under ambient conditions. A radical-mediated reaction, for example, homolytic cleavage of the C–O bond of esters (path D), may also be possible, because the reaction in SCW is conducted at high temperature.

To clarify the mechanism, we performed kinetic studies on the hydrolysis of methyl 2-phenylpropionate (**1**) in SCW at 390 °C and various water densities. This compound was



Scheme 1. Possible mechanisms of ester hydrolysis in SCW.

[*] Prof. S. Yamago, Prof. J. Yoshida
Department of Synthetic Chemistry and Biological Chemistry
Graduate School of Engineering, Kyoto University
Kyoto 606-8501 (Japan)
Fax: (+81) 75-753-5911
E-mail: yamago@sbchem.kyoto-u.ac.jp
yoshida@sbchem.kyoto-u.ac.jp

Prof. O. Kajimoto, Dr. H. Oka
Department of Chemistry
Graduate School of Science, Kyoto University
Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-3974
E-mail: kajimoto@kuchem.kyoto-u.ac.jp

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selected so that hydrolysis via the radical pathway involving direct C–O cleavage could be detected by means of the radical-clock decarbonylation reaction of the acyl radical intermediate.^[12] We also examined the effect of protons and hydroxide ions to clarify their catalytic role. In sharp contrast to the previous mechanistic proposal, we found that hydroxide ions indeed catalyze ester hydrolysis in SCW. Among organic reactions in SCW, those catalyzed by hydroxide ions are less common than those catalyzed by protons. Therefore, our results shed new light on the mechanisms of organic reactions in SCW.

We first examined the hydrolysis of **1** in SCW [Eq. (1)] in a cylinder-type reactor at 390 °C and a water density of 0.34 g cm⁻³ for 4 min, and the reaction mixture was analyzed by GLC (gas–liquid chromatography), GC-MS (gas chromatography–mass spectrometry), and NMR spectroscopy.^[13] The ester mainly yielded carboxylic acid **2**, methanol, and a small amount of ethylbenzene. Analysis of gaseous products revealed the formation of carbon dioxide, but carbon monoxide could not be detected at all. The absence of carbon monoxide indicates that the direct homolysis of the C–O bond is unlikely. We also found that carboxylic acid **2** transformed into ethylbenzene under the above reaction conditions with the loss of carbon dioxide [Eq. (1)].^[14] Although the cylinder-type reactor was suitable for product characterization, the reproducibility of the product yields was low. Therefore, detailed kinetics were examined with a flow-type reactor.

The hydrolysis of **1** in the flow-type reactor was carried out at 390 °C and water densities from 0.26 to 0.57 g cm⁻³ for

0.3–3.1 min, and the products and recovered **1** were analyzed by GLC.^[15] The solution of **1** [(2.5–3.8) × 10^{−3} M] was homogeneous even in ambient water and hence would remain homogeneous under the reaction conditions, because SCW dissolves organic compounds more readily than ambient water. The sum of **2**, ethylbenzene, and recovered **1** was 80–90% in all cases, and various uncharacterized low molecular weight products were also detected by GLC.

We also analyzed the first-order kinetics of the decarboxylation of **2** in SCW under similar conditions to evaluate the rate constant k_3 . We obtained the pseudo-first-order rate constant k_1 for the hydrolysis of **1** according to Equations (2) and (3) under the assumption that the formation of the

$$\frac{d[\mathbf{1}]}{dt} = -(k_1 + k_2)[\mathbf{1}] \quad (2)$$

$$\frac{d[\mathbf{2}]}{dt} = k_1[\mathbf{1}] - k_3[\mathbf{2}] \quad (3)$$

uncharacterized products takes place with a rate constant k_2 via an independent pathway. The results are summarized in Table 1. The most striking feature in Table 1 is that k_1 increases significantly with increasing pressure p and density ρ , while k_2 does not change (entries 1–5 and Figure 1). This observation partially proves the assumption that the uncharacterized products were formed via independent pathways.

Table 1. Hydrolysis of **1** in SCW at 390 °C [Eq. (1)].

Entry	p [MPa]	ρ [g cm ^{−3}]	$k_1 + k_2$ [a]	k_1 [a]	k_2 [a]	k_3 [a]	k_1' [b]
1	25.7	0.260	2.23	0.58	1.65	3.77	56.7
2	26.7	0.344	2.94	1.21	1.73	2.32	12.6
3	28.3	0.427	4.34	2.53	1.80	2.28	4.68
4	33.0	0.510	6.99	6.61	0.39	2.57	2.95
5	41.1	0.568	11.0	10.3	0.71	2.47	1.95
6 ^[c]	28.3	0.427	3.57	1.78	1.79	2.28	n.d. ^[d]
7 ^[e]	28.3	0.427	3.91	2.12	1.79	2.28	n.d. ^[d]

[a] × 10^{−3} s^{−1}. [b] × 10⁴ L mol^{−1} s^{−1}. [c] The reaction was carried out in the presence of 0.8 equiv of **2**. [d] Not determined. [e] The reaction was carried out in the presence of 1.6 equiv of **2**.

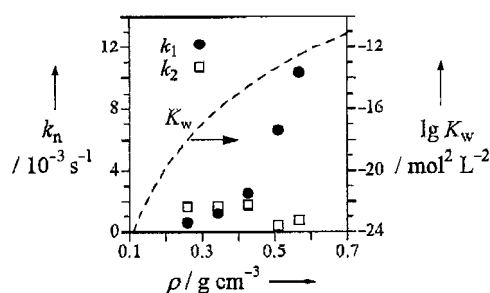


Figure 1. Rate constants k and the ionic product of water (K_w) as functions of the water density ρ . Correlation between the rate constant k_1 and the ionic product of water (K_w).

To clarify the origin of the observed density-dependent increase in k_1 , we examined the correlation between k_1 and the ionic product of water (K_w), because K_w is also a function of the water density ρ , as is shown in Figure 1 (dotted line).^[16]

We found that k_1 has a linear correlation with the square root of K_w ($k_1 = k_1' K_w^{0.5}$; k_1' is the intrinsic rate constant), as shown in Figure 2.^[17] As the square root of K_w is proportional to $[H^+]$ and $[OH^-]$, which catalyze ester hydrolysis under ambient conditions, the observed good correlation strongly suggests that the proton or the hydroxide ion dissociated from SCW promotes the hydrolysis.

To determine the catalytic species, we examined the effects of protic acid on the rate by adding **2** and found that it had no effect on the rate (Table 1, entries 6 and 7). Under the conditions of entry 7, the initial proton concentration from dissociation of SCW was calculated to be 5.4×10^{-8} mol L^{−1}^[16] and that from dissociation of **2** was 3.3×10^{-7} mol L^{−1}, by assuming that the dissociation constant of **2** is similar to that of 2-naphthoic acid in SCW.^[10] Therefore, the results clearly indicate that protons have no effect on the hydrolysis under these conditions, and that hydroxide ions indeed catalyze the hydrolysis.^[18]

Our conclusion seems to disagree with the previous report by Krammer and Vogel^[9] on a rate enhancement by adding carboxylic acid. However, we believe that the discrepancy can be attributed to the concentration of the substrates; the initial concentration of the substrate and the added acid in our experiments is approximately 100–200 times lower than that of Krammer and Vogel.^[19] Therefore, the effect of the protons generated from the carboxylic acid is negligible under our reaction conditions. Because the base-catalyzed hydrolysis proceeds about 1000 times faster than the acid-catalyzed hydrolysis under ambient conditions,^[20] it is not surprising that the hydroxide ion catalyzed regime dominates over the proton-catalyzed one until the proton concentration from dissociation of the carboxylic acid greatly exceeds that of the hydroxide ions. Therefore, the hydroxide ion catalyzed reaction dominates over the proton-catalyzed reaction in the initial stage of the hydrolysis or under dilute conditions.

We also found that the rate of the hydrolysis was strongly affected by the dielectric constant ϵ . When we plotted the logarithmic intrinsic rate constant k_1' against the Kirkwood polarity parameter $(\epsilon - 1)/(2\epsilon + 1)$,^[21] we observed an excellent linear correlation (Figure 3). The negative linear coefficient indicates that the rate of hydrolysis decreases with increasing dielectric constant. This result can be explained by considering the differences in charge localization between the reactants and the transition state (TS). Since the negative charge is more delocalized in the TS than

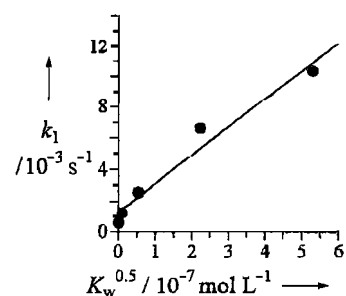


Figure 2. Correlation between the rate constant k_1 and the ion product of water K_w .

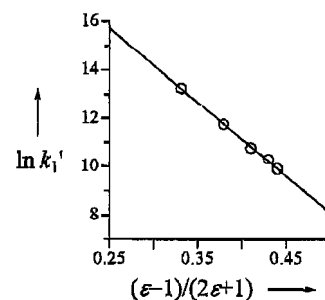


Figure 3. Correlation between the intrinsic rate constant k_1' and the Kirkwood polarity parameter.

in the reactants, the polar media must stabilize the reactants more efficiently than the TS. Consequently, the hydrolysis rate decreases with increasing water density.

In summary, we have demonstrated that the hydrolysis of esters takes place exclusively by ionic mechanisms, whereby hydroxide ions dissociated from SCW catalyze the reaction. This mechanism is dominant in the initial stage of the reaction, since the concentration of the generated carboxylic acid is low. As the concentration of carboxylic acid increases with the progress of the reaction, the mechanism would change to the proton-catalyzed reaction if the concentration of substrates were sufficiently high.^[9] Our results clearly indicate that one must consider the involvement of hydroxide ions in other reactions in SCW, because dissociation of water produces the same amount of protons and hydroxide ions.

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- [18] Addition of sodium hydroxide ($4.8 \times 10^{-7} \text{ mol L}^{-1}$) enhanced the rate of hydrolysis by a factor of about 2.5. However, the lack of data on the dissociation constant of sodium hydroxide in SCW and the difficulties in obtaining an accurate value of k_3 prevented our making detailed kinetic analyses.
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Modular Ligands for Asymmetric Synthesis: Enantioselective Catalytic Cu^{II}-Mediated Condensation Reaction of Ethyl Pyruvate with Danishefsky's Diene**

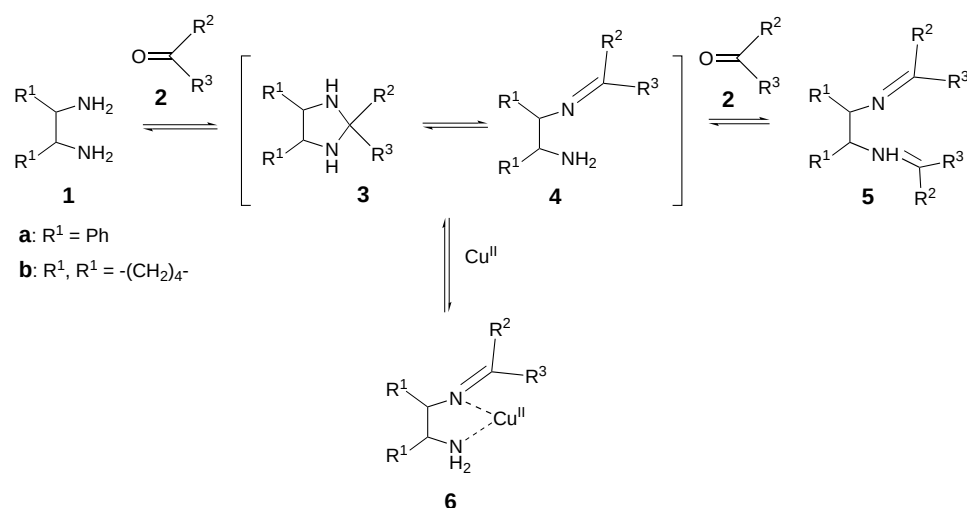
Peter I. Dalko,* Lionel Moisan, and Janine Cossy*

The search for new catalysts for asymmetric synthesis is an area of significant importance in modern organic synthesis, and a number of spectacular advances have been reported in recent years.^[1–2] However, there is still a need for simple and readily available catalysts, particularly for C–C bond-forming processes.^[3] A modular system that allows quick access to a great diversity of ligands from simple components is valuable. Peptide-based ligands have been developed for Ti-catalyzed additions of TMSCN to *meso* epoxides^[4] and imines (Strecker amino acid synthesis),^[5] and Zr-catalyzed addition of dialkylzincs to imines.^[6] Recently, peptide-based phosphane ligands have been shown to promote efficient Cu-catalyzed conjugate addition.^[7] Moreover, this class of ligands allows the regio- and enantioselective formation of quaternary carbon centers by using allylic reagents.^[8] We report herein a simple and efficient approach that leads to the generation of a great diversity of asymmetric ligands from easily available components.^[9]

The catalyst preparation is based on the condensation of 1,2-diamines^[10] of type **1** with ketones or aldehydes **2** (Scheme 1), which affords imidazolidines **3** in solution in equilibrium with the open form **4**. The corresponding bis-imine **5** and the starting diamine **1** are often present with compounds **3** and **4** in the reaction mixture.^[11] We anticipated that chelating metals such as Cu^{II} would shift this equilibrium toward the metallacyclic form **6** by forming a bidentate complex (Scheme 1).^[12] Although no precedent for the use of

[*] Dr. P. I. Dalko, Prof. Dr. J. Cossy, L. Moisan
Laboratoire de Recherches Organiques associé au CNRS, ESCPI
10 rue Vauquelin, 75231 Paris Cedex 05
Fax: (+33)1-40-79-46-60
E-mail: peter.dalko@espci.fr, janine.cossy@espci.fr

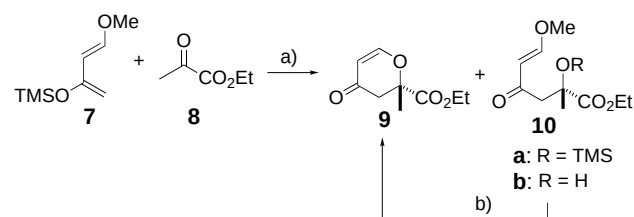
[**] The Association pour la Recherche contre le Cancer (ARC) (grant no. 7579) is gratefully acknowledged for financial support.



Scheme 1. Condensation reaction between vicinal diamines and carbonyl compounds.

this type of ligand in enantioselective catalytic reactions has been reported, analogous reactions in the literature suggest that these complexes may be active in a number of reactions.^[13]

To demonstrate the practical use of the catalyst system, a condensation reaction between *trans*-1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene (**7**; Danishefsky's diene) and ethyl pyruvate (**8**) was selected (Scheme 2).^[14, 15] In this reaction,



Scheme 2. Reaction between Danishefsky's diene and ethyl pyruvate by using chiral Cu^{II} -derived catalysts. Reagents and conditions: a) $\text{Cu}^{\text{II}}-\text{L}^*_n$ (10%), 4-Å molecular sieves, THF, -72°C , 72 h; b) CF_3COOH (cat.), room temperature.

dihydropyrrone **9** can be formed through two distinct mechanistic pathways, that is, through a traditional hetero-Diels–Alder (HDA) cycloaddition reaction or by a Mukaiyama aldol condensation pathway followed by cyclization.^[16] It is generally accepted that the Mukaiyama aldol product **10** can either be isolated, or may undergo a ring-closure reaction to give dihydropyrrone **9** under the reaction conditions or by treatment with acid. Herein we show that complexes derived from chiral diamines, carbonyl compounds, and Cu^{II} salts catalyze both reaction pathways and afford the desired adducts with high enantiomeric excesses.

The ligands were prepared by the condensation of amines **1** (Scheme 1) with ketones or aldehydes (see Table 1).^[17] The chiral Lewis acid catalysts were obtained by adding a stoichiometric amount of $\text{Cu}(\text{OTf})_2$ to the reaction mixture, which was allowed to stand for 16 h at room temperature (premixing).^[18] The premixing time significantly influenced the enantioselectivity of the condensation reaction. In gen-

eral, a lower *ee* value was obtained for dihydropyrrone **9** when the premixing time was reduced (see below).

The condensation reaction between **7** and **8** in the presence of the chiral complexes derived from diamines **1a** and **1b** (10 mol %), carbonyl compounds **2a–f**, and copper(II) salt at -72°C afforded dihydropyrrone **9** and the Mukaiyama aldol product **10** (Scheme 2). At this stage, the *ee* value of the primary cycloadduct **9** was determined^[19] (Table 1), but unfortunately the *ee* values of **10a** and **10b** could not be determined.

The mixture of **9** and **10** was converted into the dihydropyrrone **9** by treatment with a catalytic amount of triflic acid, and the *ee* value of the resulting dihydropyrrone was measured (Table 1).^[20]

Table 1. Condensation of **7** and **8** by using Cu^{II} complexes derived from chiral amine.

Entry	Amine 1	Ketone 2	1/2	yield [%]	9 <i>ee</i> [%] ^[a]	<i>ee</i> [%] ^[b]
1	(–)- 1a	none		0	–	–
2	(–)- 1a	cyclohexanone (2a)	1:1	72	70	(92)
3	(–)- 1a	cyclopentanone (2b)	1:1	85	91	(92)
4	(–)- 1a	cyclobutanone (2c)	1:1	85	94	(≥ 98)
5	(–)- 1a	(–)-menthone (2d)	1:1	63	10	(10)
6	(+)- 1a	(–)-menthone (2d)	1:1	61	12	(17)
7	(–)- 1a	acetone (2e)	1:1	67	54	(70)
8	(–)- 1a	benzaldehyde (2f)	1:1	80	5	(18)
9	(–)- 1a	benzaldehyde (2f)	1:2	< 2	–	–
10	(–)- 1b	cyclohexanone (2a)	1:1	0	–	–

[a] The *ee* values after treatment with acid. [b] The *ee* values before treatment with acid. Reaction conditions: THF, catalyst (10%), -72°C , 4 Å molecular sieves, 72 h.

As expected, the diamine–copper(II) triflate complex was inefficient in mediating the reaction (Table 1, entry 1). When ligands derived from diamine (–)-**1a** and cyclohexanone **2a** were used (Table 1, entry 2) the reaction afforded the hetero-Diels–Alder product **9** with high *ee* (92 %). However, after treatment with triflic acid, the enantiomeric excess of **9** proved to be lower (*ee* 70 %).^[20, 21] When the complexation time (premixing) was reduced from the usual 16 h (Table 1, entry 2) to 1 h, **9** was obtained in identical chemical yield, but the *ee* value dropped from 70 % to 49 %.

Upon decreasing the ring size of the ketone component from five to four carbon atoms, the *ee* value of cycloadduct **9**, before treatment with acid, increase from 92 % (Table 1, entry 3) to better than 98 % (Table 1, entry 4). Likewise, the *ee* value of **9** after treatment with acid increased from 91 % (Table 1, entry 3) to 94 % (Table 1, entry 4). Somewhat surprisingly, low enantioselectivity (10 %) was observed when (–)-menthone was used in combination either with the (1*R*,2*R*)- or with the (1*S*,2*S*)-diphenylethylene diamine

(Table 1, entries 5 and 6). This lack of selectivity may be a consequence of the increased steric hindrance in the proximity of the metal center in **6**, which implies less selective reaction paths. Interestingly, acyclic ketones such as acetone **2e** were shown to be less selective than cyclic ketones (Table 1, entry 7). Also, imidazolidines derived from diamine and benzaldehyde **2f** resulted in low enantioselectivity (Table 1, entry 8). Although bis-imines of type **5** were shown earlier to be efficient in promoting enantioselective copper(II)-mediated HDA reactions,^[2a] the bis-benzyl imine–copper complex derived from **1a** and **2f** afforded only traces of a nearly racemic product **9** under standard conditions (Table 1, entry 9).^[22] Furthermore, ligands derived from **1b** and **2a** promoted neither the formation of the HDA adduct nor the Mukaiyama aldol product (Table 1, entry 10).

The Cu^{II}/ligand stoichiometry was critical to the selectivity and reactivity. This dependence was monitored on the HDA adduct **9**.^[23] Whereas a 1:1 ratio of cyclohexylidene ligand derived from (–)-**1a**, **2a**, and Cu(OTf)₂ afforded **9** in 92 % *ee*, an increase in the Cu^{II}/ligand ratio to 2:1 resulted in only 73 % *ee*. On the other hand, when a twofold molar excess of ligand relative to the Cu^{II} salt was used, the catalytic activity of the complex was inhibited.

The vicinal diamine ligands can be replaced by a chiral α -aminoalcohol. Although this reaction was not optimized, a reversal in enantioselectivity of the dihydropyrene **9** (67 % yield, 35 % *ee*) from that of the Mukaiyama aldol product **10** was observed when (*R*)-phenylglycinol (**11**) was used.

The foregoing three-component catalyst systems provide a simple and effective approach for generating a variety of structurally diverse chiral complexes for use in asymmetric synthesis. Important structural features responsible for the catalytic activity are unknown at the present time. The operational simplicity, easy availability, low cost, stability, and diversity of potentially active organometallic structures all contribute to the potential usefulness of these catalysts.

Experimental Section

Diamine **1** (0.09 mmol, 0.1 equiv) and ketone **2** (0.09 mmol, 0.1 equiv) were dissolved in a small amount of dichloromethane (2 mL). After 4 h at room temperature, the solvent was evaporated, and the residue was co-evaporated twice with benzene. Cu(OTf)₂ (32.6 mg, 0.09 mmol, 0.1 equiv) and the ligand were introduced in a dry flask with a small amount of ground 4-Å molecular sieves (ca. 100 mg), and THF (1.5 mL) was added to the solid through a cannula. The slurry was stirred under an inert atmosphere of Ar for 16 h at room temperature. The slurry was cooled to –72 °C, ethyl pyruvate (100 μ L, 0.9 mmol, 1.0 equiv) and Danishefsky's diene (215 μ L, 1.3 mmol, 1.2 equiv) were added in one portion through a syringe, and the mixture was stirred for an additional 72 h at –72 °C. Trifluoroacetic acid (0.1 mL) was then introduced to the mixture, which was allowed to warm to room temperature. After 12 hours, the solution was neutralized with saturated sodium bicarbonate, the organic phase was separated, and the aqueous phase was extracted with dichloromethane (2 $\times$ 10 mL). The combined organic phases were dried over Na₂SO₄, the solvent was evaporated, and the crude reaction mixture was purified on a short column of silica gel (pentane/ethyl acetate 4:1 eluent). *R*_f = 0.5 (silica gel, EtOAc/pentane 1:1); IR (film): $\tilde{\nu}$ = 1740, 1680, 1600 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz): δ = 7.36 (d, *J* = 5.9 Hz, 1H), 5.42 (d, *J* = 5.9 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.00 (d, *J* = 16.5 Hz, 1H), 2.68 (d, *J* = 16.5 Hz, 1H), 1.66 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ = 190.1, 171.0,

161.9, 107.4, 82.9, 62.4, 44.8, 24.2, 14.1; MS (EI, 70 eV): *m/z*: 184 (27), 111 (100), 110 (24), 86 (12), 71 (89), 69 (25).

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- [19] The *ee* value of **9** was determined by chiral GC-MS on a Crompack Chirasil-DEX CB column.
- [20] No epimerization of **9** was observed after treatment with acid.
- [21] The absolute configuration of the newly formed stereogenic center of **9** was found to be *R* in each case when the (1*R*,2*R*)-diphenylethylene diamine ligand was used. The absolute configuration was determined by comparison of the optical rotation of **9** with the literature value.^[15c]
- [22] The ligand was prepared by condensation of benzaldehyde (2 equiv) with **1a** followed by addition of $\text{Cu}(\text{OTf})_2$ (1 equiv).
- [23] The reaction was quenched at -72°C by using trifluoroacetic acid and was allowed to stir at -10°C for 1 h. This workup procedure allowed the isolation of the HDA and aldol products. No interconversion between the aldol and HDA products was observed under these conditions.

A Thermotropic Mesophase Comprised of Closed Micellar Aggregates of the Normal Type**

Petra Fuchs, Carsten Tschierske,* Klaus Raith, Kumar Das, and Siegmar Diele

The ability of amphiphilic molecules to self-organize in aqueous systems with formation of micelles, vesicles, and lyotropic mesophases is of great importance for numerous applications of surfactants in several fields of science and technology, and it is also a prerequisite for the development of biological structures.^[1, 2] In these polymolecular assemblies the hydrophilic parts (together with the solvent molecules) and the lipophilic parts of the amphiphiles are segregated into nanoscopic compartments, whereby changing the degree of curvature of the interfaces between the incompatible nano-

phases gives rise to a sequence of different mesophase morphologies. Hence, in dependence on the amphiphile structure, its concentration, and the temperature, different lyotropic mesophases can result.^[1–3] Arrays of alternating layers yield smectic phases (*SmA*), regular arrangements of cylinders give rise to hexagonal columnar phases (*Col_h*), and closed globular or nonglobular micelles can form cubic mesophases (micellar cubic phases, *Cub_I*). Another type of cubic mesophase, consisting of two mutually interwoven networks of branched cylinders (bicontinuous cubic mesophases, *Cub_V*), occurs at the transition between smectic and columnar organization (Figure 1). For each of the nonlamellar mesophases two different types are possible. In normal phases (type 1, positive curvature of the polar/apolar interface), the stronger cohesive forces (hydrogen bonds) are located in the continuum surrounding the aggregates. In the reversed (or inverse) phases (type 2, negative interface curvature) they are

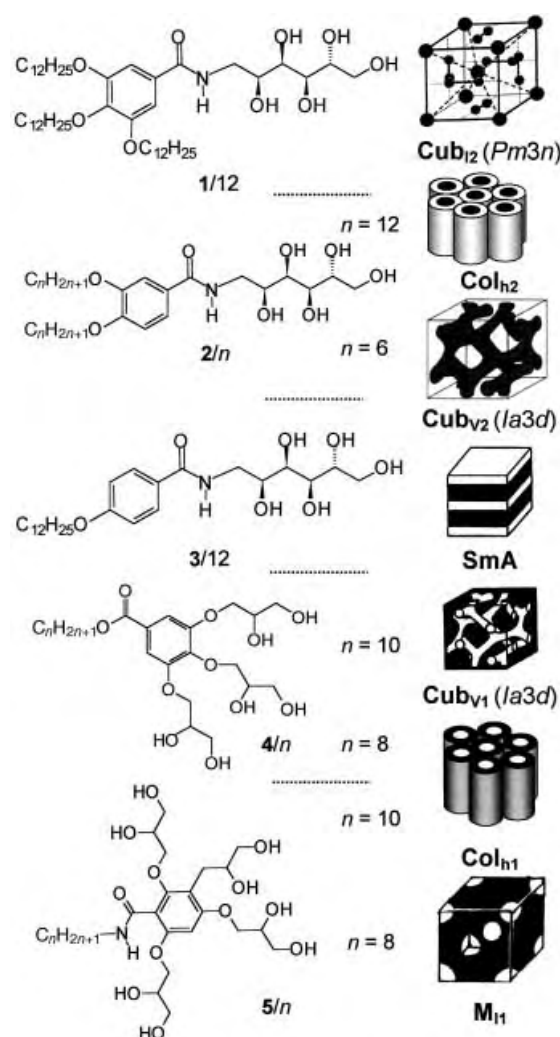


Figure 1. Dependence of the mesophase morphology of different poly-hydroxy amphiphiles on the molecular structure. Abbreviations: *Cub₁₂* = reversed discontinuous (micellar) cubic mesophase with *Pm3n* lattice; *Col_{h2}* = reversed hexagonal columnar mesophase; *Cub_{v2}* = reversed bicontinuous cubic mesophase with *Ia3d* lattice; *SmA* = smectic A-phase; *Cub_{v1}* = normal-type bicontinuous cubic mesophase with *Ia3d* lattice; *Col_{h1}* = normal-type hexagonal columnar mesophase; *M₁₁* = mesophase comprised of discrete direct micelles with unknown lattice (the *Im3m* lattice is shown as one of the possible structures).

[*] Prof. Dr. C. Tschierske, Dr. P. Fuchs
Institute of Organic Chemistry
Martin-Luther-University Halle – Wittenberg
Kurt-Mothes-Straße 2, 06120 Halle (Germany)
Fax: (+49) 345-55-27223
E-mail: tschierske@chemie.uni-halle.de

Dr. S. Diele, Dr. K. Das
Institute of Physical Chemistry
Martin-Luther-University Halle – Wittenberg
Mühlpforte 1, 06120 Halle (Germany)
Fax: (+49) 345-55-27157

Dr. K. Raith
Faculty of Pharmacy
Martin-Luther-University Halle – Wittenberg (Germany)

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located inside the aggregates. The same phase sequence was found for binary AB diblock copolymers, which can be regarded as high molecular weight relatives of surfactants. Here, the phase sequence depends on the volume fractions of the two chemically connected, but incompatible polymer blocks.^[4]

To confirm the generality of this sequence of distinct morphologies, it was a challenge to realize the same phase sequence in a series of low molecular weight amphiphiles in the absence of any solvent. Polyhydroxy amphiphiles are especially useful for this purpose, because they allow the precise control of the mesophase morphology by adjusting the molecular shape, the polar/apolar parity, and the attractive forces (hydrogen bonding), simply by changing the number and position of the alkyl chains and hydroxy groups.^[5–9] Previously, all reversed-type mesophases (**1–3** in Figure 1),^[7] as well as the normal-type bicontinuous cubic (Cub_{v1}) phase and the normal-type hexagonal columnar (Col_{h1}) mesophase (compounds **4**),^[9] were realized with these materials. Now we have successfully completed this series, and here we report a novel thermotropic mesophase comprised of normal-type discrete micelles.

To achieve such a phase structure we synthesized compounds **6/n** and **5/n**, in which, respectively, three and four propane-2,3-diol units are attached to an aromatic linking unit such that the hydroxy groups can completely surround the aromatic core. These compounds were obtained as shown in Scheme 1. The allylation^[10] of methyl 2,4,6-trihydroxybenzoate led to a 3:1 mixture of the tris(allyl ether) **7** and the

product of additional C-allylation^[11] (**8**). These were separated by chromatography and transformed into the final compounds **5/n** and **6/n** as shown in Scheme 1.^[12–14]

The obtained compounds (see Table 1)^[15, 16] were first investigated by polarizing microscopy and differential scanning calorimetry (DSC). No mesophase could be detected for **6/8**, whereas a spherulitic texture, as is typical for hexagonal

Table 1. Transition temperatures T [°C] and corresponding enthalpy values ΔH [kJ mol⁻¹] (lower lines) of **5/n** and **6/n**.^[a]

Comp.	T [°C]	
	ΔH [kJ mol ⁻¹]	
5/8	Cr 84 (M ₁₁ 55) Iso	
	22.4	0.8
5/9	Cr 91 (Col _{h1} 80) Iso	
	43.1	1.1
5/10	Cr 86 Col _{h1} 118 Iso	
	20.2	1.1
6/8	Cr 99 Iso	
	48.0	
6/10	Cr 109 (Col _{h1} 95) Iso	
	44.6	0.8

[a] Abbreviations: Cr = crystalline solid state; Iso = isotropic liquid phase; for the other abbreviations, see Figure 1. Transition temperatures and enthalpies were determined by DSC (Perkin-Elmer DSC-7, first heating scan, rate: 10 K min⁻¹) and confirmed by polarizing optical microscopy. Values in parentheses refer to monotropic (metastable phases), which were determined in the second heating scan.

columnar phases, was observed after supercooling a melt of **6/10**. Compound **5/10** with four diol groups shows an enantiotropic (thermodynamically stable) hexagonal columnar mesophase. X-ray scattering confirmed this phase assignment (diffuse wide-angle scattering and three sharp reflections in the small-angle region, the positions of which correspond to $1:3^{1/2}:5^{1/2}$; $a_{\text{hex}} = 3.87$ nm at $T = 100$ °C). The diameter of the columns (3.87 nm)^[17] is in good agreement with an organization of the strongly coiled fluid alkyl chains in cylinders with a surrounding corona of hydrogen-bonding networks (Col_{h1}, see Figure 2).^[18] Compound **5/9**, which is one CH₂ unit shorter than **5/10**, also forms a columnar phase, but with significantly lower mesophase stability.

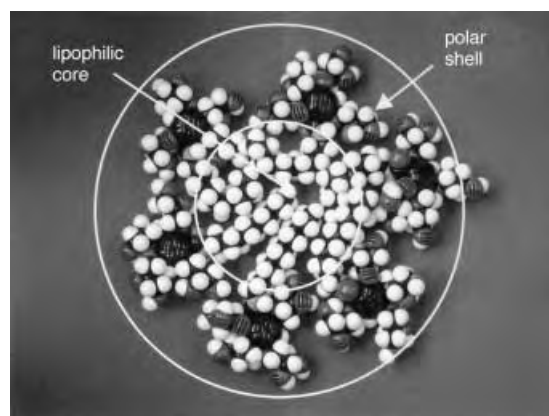
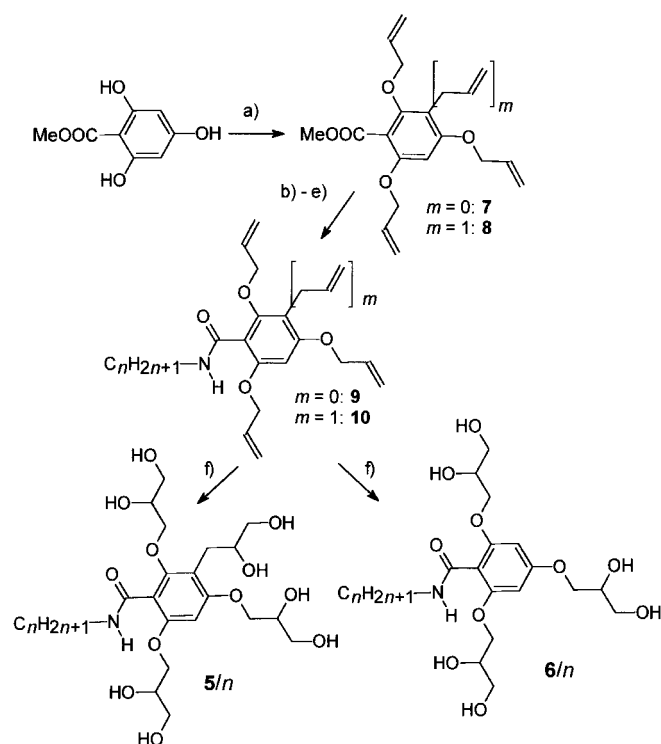


Figure 2. Cross section through a column of the Col_{h1} phase of **5/10**. A related picture would be found for the cross section through spherical micelles of the M₁₁ phase of **5/8**.



Scheme 1. Synthesis of compounds **5/n** and **6/n**. a) BrCH₂CH=CH₂, K₂CO₃, DMF, 100 °C, 10 h; b) chromatographic separation of **7** and **8**; c) NaOH, DMSO, H₂O, 60 °C, 6 h;^[12] d) HOC₆F₅, dicyclohexylcarbodiimide, THF, 25 °C, 14 h;^[13] e) C_nH_{2n+1}NH₂, CH₂Cl₂, 25 °C, 12 h; f) *N*-methylmorpholine *N*-oxide, cat. OsO₄, acetone, H₂O, 25 °C, 48 h.^[14]

Compound **5/8** behaves quite differently. The first DSC heating scan shows only a broad endotherm with a maximum at 84 °C which corresponds to a melting process. On cooling at 2 K min⁻¹ an exotherm with a rather small enthalpy ($\Delta H = -0.8$ kJ mol⁻¹) can be found at 33 °C followed by a glass transition at 15 °C. In the second heating scan, after the glass transition at 18 °C, an endotherm with equal enthalpy to the phase transition in the cooling scan is found at 55 °C (see Figure 3). Investigation by polarized light microscopy reveals

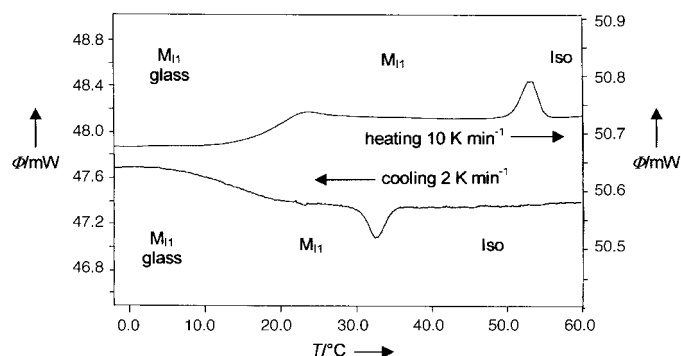


Figure 3. DSC heating (second heating scan) and cooling scan of compound **5/8**. The heat flow Φ on the left-hand side corresponds to the heating scan, and that on the right-hand side to the cooling scan; for abbreviations, see Figure 1.

that on cooling the isotropic liquid phase becomes rather viscous at 30–35 °C. On heating, the viscosity decreases at about 50–55 °C. These observations indicate the presence of an optically isotropic mesophase (M) which undergoes a transition to the liquid state at circa 55 °C and vitrifies slightly below room temperature. Although this mesophase is only monotropic (metastable), crystallization occurs only after prolonged storage (several days) above the glass transition temperature. Not only the crystallization, but also the transition from the liquid state to this mesophase can be significantly supercooled; this is typical for cubic mesophases and points to the presence of a three-dimensional lattice within this mesophase.

To obtain further information on the structure of this mesophase we investigated the contact region of **5/8** with **4/10**, for which a type 1 bicontinuous cubic mesophase (Cr 75 Cub_{V1} 108 Iso, see Figure 1) was confirmed in earlier work.^[9b] In the contact region between these two compounds a concentration gradient develops. A birefringent mesophase with a spherulitic texture typical of hexagonal columnar phases is induced between < 20 °C and 96 °C, and separates the mesophase of **5/8** and the Cub_{V1} phase of **4/10** (see Figure 4). The replacement of the type 1 bicontinuous cubic phase of **4/10** by a columnar mesophase (Col_{h1}) indicates that the polar/apolar interface curvature becomes more positive with increasing concentration of **5/8**.^[19] This means that in the isotropic mesophase of **5/8** the polar/apolar interface should be more strongly curved than in the columnar phase, and this confirms that the mesophase of **5/8** is composed of discrete type 1 micellar aggregates (M_{II}). These spheroidal aggregates comprise the alkyl chains surrounded by the polar parts of the molecules, which form a continuous hydrogen-bonding network around

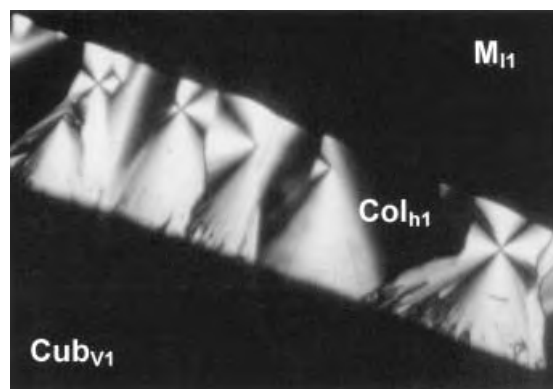


Figure 4. Hexagonal columnar phase developing in the contact region between the bicontinuous cubic phase of **4/10** (Cub_{V1}) and the isotropic mesophase of **5/8** (M_{II}), as observed between crossed polarizers at 50 °C.

them. X-ray scattering investigations, performed with a Guinier film camera and a goniometer, should provide information about the organization of these micelles in the optically isotropic mesophase of **5/8**. A diffuse scattering in the wide-angle region (maximum at $d = 0.42$ nm) confirms the liquidlike disordered state of the alkyl chains and the hydrogen bonding networks. In the small-angle region, rather diffuse scattering can also be found, but sometimes three sharp nonequidistant reflections, corresponding to $\theta_1 = 1.57^\circ$, $\theta_2 = 2.72^\circ$ and $\theta_3 = 4.07^\circ$ can be observed instead (see Figure 5). The positions of these sharp reflections and their

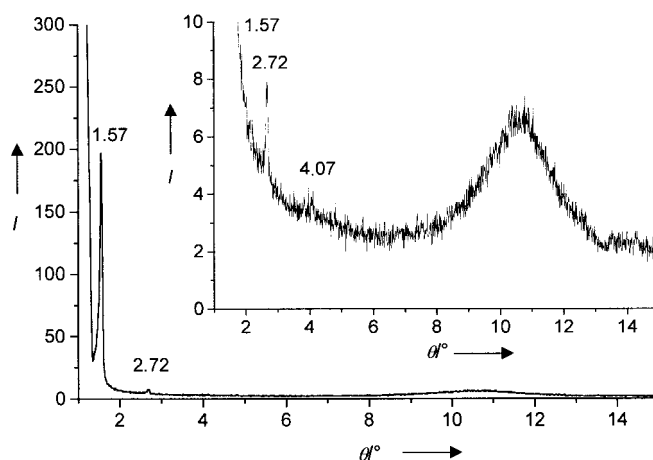


Figure 5. X-ray diffraction pattern of the M_{II} phase of **5/8** at 40 °C.

relative intensities are quite distinct from the three most intensive reflections typically found in the diffraction pattern of the $Pm3n$ lattice which is most often observed for micellar cubic phases of type 1 lyotropic systems and for the thermotropic type 2 micellar cubic mesophases of polyhydroxy amphiphiles **1/n**^[7b-d] and dendritic molecules.^[20] Instead, an assignment of these reflections is possible on the basis of a hexagonal lattice ($hk = 01, 11, 21$). However, a hexagonal arrangement of columns can be excluded because of the optical isotropy of this mesophase and the results of the miscibility studies. Therefore, we can assume a close cubic packing ($Fm3m$ or $Im3m$) or a three-dimensional hexagonal

packing of spherical micelles ($P6_3/mmc$),^[21] but the small number of reflections did not allow a certain assignment to one of these possibilities. As mentioned above, the occurrence of a superstructure in the M_{II} phase is highly sensitive to the experimental conditions and can only occasionally be found in the X-ray diffraction experiments. It is often distorted, so that in most cases only a short-range ordered structure, characterized by a rather diffuse primary peak and its higher order was recorded.^[22] This micellar mesophase can be frozen into the glassy state to furnish a (ordered or disordered) micellar glass phase below 18 °C.

In summary, a novel thermotropic mesophase, comprised of normal-type micellar aggregates has been obtained for the first time for a low molecular weight amphiphile in the absence of water or any other solvent. Thus, all main aggregate types known from aqueous lyotropic systems have successfully been realized as their thermotropic analogues within a single series of structurally related amphiphiles (**1–5**, see Figure 1). These investigations confirm that water is not necessary for the occurrence of any of the aggregate morphologies known from aqueous systems. However, because of the unique combination of organizing forces and mobility in liquid water, it can significantly increase the number of low molecular weight amphiphiles capable of forming organized soft matter.

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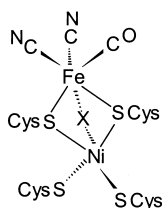
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 - [16] All compounds **4–6** are complex mixtures of diastereomers. This structural diversity is in our case helpful, because it inhibits the rapid crystallization of the samples and therefore allows detection of the mesophases.
 - [17] The molecular length amounts to *L* = 2.5 nm in the most extended conformation.
 - [18] About six molecules are arranged on average in the cross section of a 0.45 nm thick section of the columns, which was calculated according to equation (1), wherein $\rho = 1 \text{ g cm}^{-3}$, N_A = Avogadro number, *M* = molecular mass, and *h* = 0.45 nm (which corresponds to the position of the maximum of the diffuse scattering in the wide-angle region of the X-ray pattern).
- $$n = a_{\text{hex}}^2 / 2 \sqrt{3} h (N_A / M \rho) \quad (1)$$
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**$[(C_6H_4S_2)Ni(\mu-S_3')Fe(CO)(PMe_3)_2]$:
A Dinuclear $[NiFe]$ Complex Modeling the
 $[(RS)_2Ni(\mu-SR)_2Fe(CO)(L)_2]$ Core of $[NiFe]$
Hydrogenase Centers****

Dieter Sellmann,* Franz Geipel, Frank Lauderbach,
and Frank W. Heinemann

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

Hydrogenases are indispensable for the biological energy metabolism through catalysis of the reversible redox reaction $2H^+ + 2e^- \rightarrow H_2$.^[1] Among the four types of $[NiFe]$, $[NiFeSe]$,



Scheme 1. Schematic structure of the active center from *D. Gigas* hydrogenase in the oxidized form ("X" = OH^- or O^{2-}).

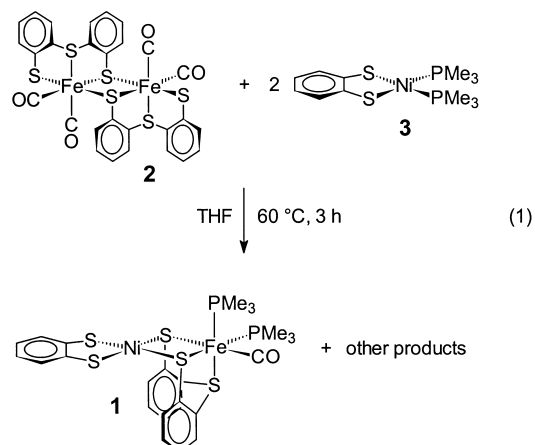
Fe-only, and metal free hydrogenases, $[NiFe]$ hydrogenases represent the majority.^[2] Their active centers contain $[Ni(S\text{-cysteinate})_4]$ units bridged to $[Fe(CN)_2(CO)]$ entities according to Scheme 1, which depicts the active center of hydrogenase from *D. gigas* in the oxidized form. "X" represents probably OH^- or O^{2-} .^[3]

In spite of the X-ray structure determination, the mechanism of $[NiFe]$ hydrogenase reactions is still poorly understood, because major questions have remained unanswered. $[NiFe]$ hydroge-

nases exist in numerous redox states designated by Ni-A, Ni-B, Ni-SU, Ni-SI, Ni-C, and Ni-R that can be labeled by their EPR spectra and individual $\nu(CO)$ frequencies.^[2a, 4] However, it is not known how these redox states are related to the metal oxidation states, where the H_2 molecule is activated and turned over, or why two different metals are needed in $[NiFe]$ hydrogenases. The relationship between $\nu(CO)$ frequencies and enzyme redox states is complicated in the sense that more reduced hydrogenase forms do not necessarily exhibit lower $\nu(CO)$ frequencies. Nickel oxidation states ranging from Ni^{III} to Ni^0 , or, contrastingly, nickel thiol species have been invoked to interpret the EPR spectra.^[2c]

To solve these questions, there have been numerous attempts aimed at the synthesis of low molecular weight complexes that model the active site of $[NiFe]$ hydrogenases. These attempts have yielded a large number of di- and oligonuclear NiFe complexes,^[5] but never afforded a complex exhibiting a $[(RS)_2Ni(\mu-SR)_2Fe(CO)(CN)_2]$ core like $[NiFe]$ hydrogenase centers. Not even analogous complexes with $[Fe(CO)(L)_2]$ entities (L = any other monodentate ligand) in place of the unique $[Fe(CO)(CN)_2]$ group could be achieved. Here we describe $[(C_6H_4S_2)Ni(\mu-S_3')Fe(CO)(PMe_3)_2]$ (**1**), the

first example of such a species ($S_3'^{2-}$ = bis(2-mercapto-phenyl)sulfide(2-)). Complex **1** resulted from the reaction of $[Fe(CO)_2(S_3')_2]$ (**2**)^[6] with labile $[Ni(PMe_3)_2(S_2')]$ (**3**),^[7] according to [Eq. (1)].



Monitoring by IR spectroscopy showed that in addition to **1** several other CO-containing complexes formed. One of them, $[Fe(CO)(PMe_3)_2(S_3')]$ (**4**), which shows a $\nu(CO)$ band at 1938 cm^{-1} (in THF), could be synthesized independently from **2** and PMe_3 ,^[8] and was completely characterized. The title complex **1** is sparingly soluble in THF and crystallized directly from the reaction solution in 20% yield.

Previous results had shown that **2** reacts with L^- = phosphane or CN^- to give stereoselectively $[Fe(CO)(L)_2(S_3')]$ complexes.^[6] In line with this, the formation of **1** can be rationalized by a sequence of steps in the course of which PMe_3 dissociates from **3** and reacts with **2** to give **4**, which subsequently adds the $[Ni(C_6H_4S_2)]$ fragments resulting from **3**. Figure 1 depicts the molecular structure of **1** as determined

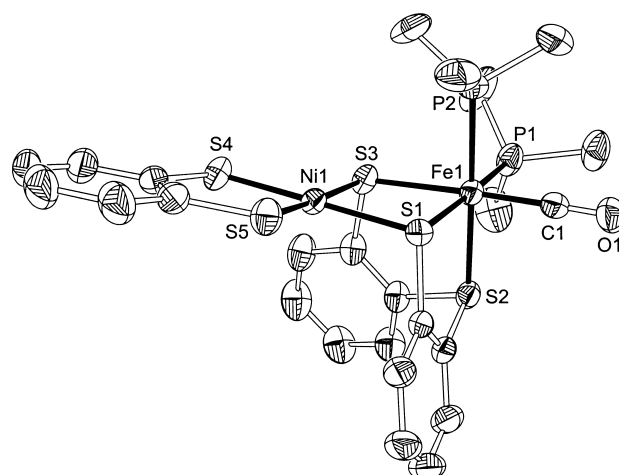


Figure 1. Molecular structure of **1** (50% probability ellipsoids; H atoms omitted). Selected distances [pm] and angles $^\circ$: Ni1-S1 224.2(1), Ni1-S3 224.0(1), Ni1-S4 215.9(2), Ni1-S5 214.1(2), Fe1-S1 230.3(1), Fe1-S2 225.4(1), Fe1-S3 231.7(1), Fe1-C1 174.8(3), Fe1-P1 226.8(1), Fe1-P2 226.7(1), Ni1...Fe1 332.3(1), S1...S3 309.1(2); S1-Ni1-S3 87.19(4), S1-Ni1-S4 178.81(5), S1-Ni1-S5 89.43(5), S3-Ni1-S4 91.80(5), S3-Ni1-S5 173.83(5), S4-Ni1-S5 91.63(5), S1-Fe1-S2 88.44(4), S1-Fe1-S3 83.98(4), S2-Fe1-S3 88.57(4), S1-Fe1-P1 175.08(4), S1-Fe1-C1 93.0(1), S3-Fe1-P1 91.46(4), P1-Fe1-C1 91.5(1), S3-Fe1-C1 177.0(1), S2-Fe1-P2 176.62(4).

[*] Prof. Dr. D. Sellmann, Dr. F. Geipel, Dipl.-Chem. F. Lauderbach, Dr. F. W. Heinemann
Institut für Anorganische Chemie der Universität Erlangen-Nürnberg
Egerlandstrasse 1, 91058 Erlangen (Germany)
Fax: (+49)9131-8527367
E-mail: sellmann@anorganik.chemie.uni-erlangen.de

[**] Transition Metal Complexes with Sulfur Ligands, Part 153. This work was supported by the Sonderforschungsbereich 583 "Redoxaktive Metallkomplexe" and the Fonds der Chemischen Industrie. Part 152: Ref. [6]. $S_3'^{2-}$ = Bis(2-mercapto-phenyl)sulfide(2-).

by X-ray crystallography, together with selected distances and angles.^[9]

The nickel center N1 is surrounded by four thiolate donors (S1, S3, S4, S5) in an essentially planar geometry, the iron center is pseudo-octahedrally coordinated. The CO ligand adopts a position *trans* to the bridging thiolate donor S3. The S1 and S3 thiolate donors of the $[\text{Fe}(\text{CO})(\text{PMe}_3)_2(\text{S}_3')]$ unit bridge the nickel and iron centers. The Ni–S distances lie in the range of 214–225 pm typical for diamagnetic four-coordinate Ni^{II} thiolate complexes.^[5, 10] The bridging Ni–S distances (223.0(1) and 224.1(2) pm), however, are distinctly longer than the terminal Ni–S distances (215.9(1) and 214.1(2) pm), possibly indicating that a dissociation of the $[\text{Ni}(\text{C}_6\text{H}_4\text{S}_2)]$ unit is facilitated. The four-membered $[\text{NiS1S3Fe}]$ ring exhibits a small dihedral angle of 11.40(6)° along the S1–S3 line. All distances and angles in the $[\text{Fe}(\text{CO})(\text{PMe}_3)_2(\text{S}_3')]$ unit are nearly identical to those found in mononuclear $[\text{Fe}(\text{CO})(\text{dppe})(\text{S}_3')]$ (dppe = 1,2-(diphenylphosphanyl)ethane).^[6] The Fe–S(thioether) distance is shorter than the Fe–S(thiolate) distances. Terminal and bridging Fe–S(thiolate) distances in mononuclear $[\text{Fe}(\text{CO})(\text{dppe})_2(\text{S}_3')]$ and dinuclear **1** differ marginally by at best 1–2 pm. In this respect, the structure of **1** reflects the remarkable structural rigidity of $[\text{Fe}(\text{S}_3')]$ fragments towards electronic effects exerted by coligands.^[6] The Ni–Fe distance of **1** (332.3(1) pm) excludes a direct Ni–Fe bond, is similar to those found for other thiolate-bridged NiFe complexes (280–370 pm),^[5] and is larger than the Ni–Fe distances found in the active sites of oxidized or reduced $[\text{NiFe}]$ hydrogenases which range from 260 to 290 pm.^[3, 11] The significance of these distances is matter of another controversial debate because theoretical calculations predict that $[\text{NiFe}]$ hydrogenases may exhibit Ni–Fe distances of up to 345 pm when associating H_2 .^[12] As judged by its ^1H and ^{31}P NMR spectra, complex **1** is diamagnetic and contains, in accordance with the route of synthesis, low-spin Ni^{II} and Fe^{II} centers. The $\nu(\text{CO})$ frequency of **1** appears at 1948 cm^{-1} (in KBr).

Synthesis, spectroscopic properties and structure of **1** permit a series of conclusions. The synthesis of **1** demonstrates that complexes containing $[(\text{RS})_2\text{Ni}(\mu\text{-SR})_2\text{Fe}(\text{CO})(\text{L})_2]$ cores can form in “self-assembly” type reactions. The spectroscopic properties of **1** enable one to assess the influence of binding a $[\text{Ni}(\text{SR})_2]$ to a $[\text{Fe}(\text{CO})(\text{CN})_2(\text{SR})_2]$ unit upon the $\nu(\text{CO})$ frequency, whether the $\nu(\text{CO})$ frequency is red- or blue-shifted, and to comment upon the controversial assignment of metal oxidation states for the various redox forms of $[\text{NiFe}]$ hydrogenases. The three complexes **1**, **4**, and **5** synthesized previously^[6] exhibit $\nu(\text{CO})$ frequencies in KBr at 1948 cm^{-1} (**1**), 1932 cm^{-1} (**4**), and 1924 cm^{-1} (**5**). Comparison of **4** and **5** demonstrates that replacing CN^- by PMe_3 blue-shifts the $\nu(\text{CO})$ frequency by 8 cm^{-1} . This is rationalized by the fact that PMe_3 is a poorer donor and better acceptor than

CN^- . Binding $[\text{Ni}(\text{C}_6\text{H}_4\text{S}_2)]$ to **4** further blue-shifts the $\nu(\text{CO})$ frequency by 16 cm^{-1} . This shows that the $[\text{Ni}(\text{SR})_2]$ unit withdraws electron density from the iron center of the $[\text{Fe}(\text{CO})(\text{L})_2(\text{SR})_2]$ core. Combining the $\nu(\text{CO})$ data of **1**, **4**, and **5** results in a $\nu(\text{CO})$ frequency of about 1940 cm^{-1} for the as-yet hypothetical $[(\text{C}_6\text{H}_4\text{S}_2)\text{Ni}(\mu\text{-S}_3')\text{Fe}(\text{CO})(\text{CN})_2]^{2-}$ ion. This anion nearly duplicates the donor atom set of $[\text{NiFe}]$ hydrogenase centers, hence its expected frequency of 1940 cm^{-1} would be indicative for a $\text{Ni}^{\text{II}}/\text{Fe}^{\text{II}}$ oxidation state of the active site. The $\nu(\text{CO})$ frequency of 1940 cm^{-1} corresponds to the Ni–R state of hydrogenases, which is the most reduced (“fully reduced”) state of hydrogenase, EPR silent (as is **1**), and directly involved in the turnover of H_2 .^[4]

The molecular parameters of **1** suggest the reason for the unique arrangement of two cyano and one carbonyl ligand at the iron center in $[\text{NiFe}]$ hydrogenase. One purpose of the CN^- and CO ligands is assumed to keep the Fe^{II} center in the low-spin state throughout all hydrogenase reactions.^[1b] The other one could be to warrant a tight binding of the $[\text{Ni}(\text{SR})_2]$ unit. The structure of **1** exhibits bridging Ni–S(thiolate) distances that are almost 10 pm longer than the terminal ones. Replacing PMe_3 in **1** by the more electron-donating CN^- ligands can be expected to enhance the nucleophilicity of the S_3' thiolate donors and in turn the bonding to the nickel. An identical mechanism might hold true for the hydrogenase centers, and our efforts to synthesize the dicyano derivative of **1** will be continued.

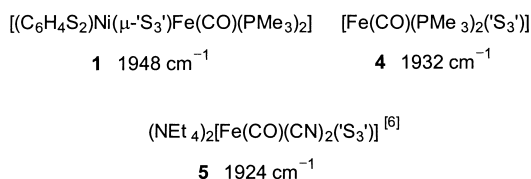
Experimental Section

All manipulations were carried out in absolute solvents under exclusion of air. $[\text{Fe}(\text{CO})_2(\text{S}_3')]_2$ ^[6] and $[\text{Ni}(\text{PMe}_3)_2(\text{S}_2')]$ ^[7] were prepared as described in the literature.

1: A THF suspension (25 mL) of $[\text{Fe}(\text{CO})_2(\text{S}_3')]_2$ (326 mg, 0.45 mmol) and $[\text{Ni}(\text{PMe}_3)_2(\text{S}_2')]$ (318 mg, 0.90 mmol) was heated to 60°C for 3 h. MeOH (60 mL) was added to the resulting dark red to black solution, and the mixture was reduced in volume by about one fourth. Black material which precipitated was removed by filtration, and the filtrate was stored at room temperature. Dark red to black crystals which crystallized from the solution were separated after two weeks, washed with Et_2O , and dried in vacuo. Yield: 114 mg (19%). IR (KBr): $\tilde{\nu} = 1948\text{ cm}^{-1}$ (CO); IR (Nujol): $\tilde{\nu} = 1952\text{ cm}^{-1}$ (CO); elemental analysis calcd (%) for $\text{C}_{25}\text{H}_{30}\text{FeNiO}_2\text{P}_2\text{S}_5$ (683.29): C 43.95, H 4.43, S 23.46; found: C 44.04, H 4.57, S 23.33. Complex **1** is sparingly soluble in all common solvents and slowly decomposes in CH_2Cl_2 or THF solution. NMR spectra could be recorded in CD_2Cl_2 . ^1H NMR (399.7 MHz, CD_2Cl_2): $\delta = 8.01$ (m, 1H; S_3'), 7.89 (m, 1H; S_3'), 7.87 (m, 1H; S_3'), 7.76 (m, 1H; S_3'), 7.38–7.23 (m, 4H; S_3'), 7.03 (m, 2H; $\text{C}_6\text{H}_4\text{S}_2$), 6.61 (m, 2H; $\text{C}_6\text{H}_4\text{S}_2$), 2.34 (d, 9H, $^2J_{\text{PH}} = 9.8\text{ Hz}$; PMe_3), 1.21 (d, 9H, $^2J_{\text{PH}} = 8.8\text{ Hz}$; PMe_3); $^{31}\text{P}\{^1\text{H}\}$ NMR (161.7 MHz, CD_2Cl_2): $\delta = 18.69$ (d, $^2J_{\text{PP}} = 47.2\text{ Hz}$), 11.67 (d, $^2J_{\text{PP}} = 47.4\text{ Hz}$) (PMe_3).

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Highly Enantioselective Preparation of Multifunctionalized Propargylic Building Blocks**

Thomas Schubert, Werner Hummel, and Michael Müller*

Optically active propargylic alcohols are versatile building blocks in the synthesis of a broad variety of natural compounds and drugs.^[1] Therefore, numerous synthetic approaches have been developed to obtain propargylic alcohols with high enantiomeric excesses. Chemical methods offer straightforward access to these compounds, for example, enantioselective reductions^[2] or asymmetric zinc-mediated additions to aldehydes,^[3] as well as enzymatic methods with oxidoreductases^[4] or lipases^[5]. Nevertheless, most published procedures do not give enantiomerically pure α,β -alkynyl-substituted methanols. Moreover, there has been only one report of a chiral α,β -alkynyl α -chloro- or α -bromohydrin. Corey and co-workers obtained (*R*)-4-triisopropylsilyl-1-chloro-3-butyn-2-ol by oxazaborolidine reduction of the corresponding ketone. However, the authors indicated that the bulky triisopropylsilyl group was essential for an *ee* of 95%.^[2c] In general, reduction methods applied to α -chloro- or α -bromo ketones need to be mild as a result of possible side reactions at the activated α position. Furthermore, zinc-mediated additions to aldehydes cannot be used for the preparation of α,β -alkynyl α -chloro- or α -bromohydrins.^[6] Nevertheless, propargylic α -chlorohydrins could be easily transformed, for example, into epoxides, thus offering novel comprehensive applications in organic syntheses.

In preceding studies, we synthesized a broad variety of enantiopure propargylic alcohols by the enzymatic reduction of alkynes.^[7] Thus, both enantiomers of α,β -alkynyl-substituted methanols are accessible. Our interest in a general approach to obtain optically pure building blocks as intermediates in organic syntheses encouraged us to continue our

[*] Dr. M. Müller, Dipl.-Chem. T. Schubert
Institut für Biotechnologie 2, Forschungszentrum Jülich GmbH
52425 Jülich (Germany)
Fax: (+49) 2461-613870
E-mail: mi.mueller@fz-juelich.de
Dr. W. Hummel
Institut für Enzymtechnologie
Heinrich-Heine-Universität Düsseldorf (Germany)

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studies towards the reduction of α -halo propargylic ketones. We report herein a straightforward approach to both enantiomers of α,β -alkynyl α -chloro- or α -bromohydrins through the enzymatic reduction of the corresponding ketones. By subsequent treatment with a mild base, the alcohols were converted into propargylic epoxides to give other highly functionalized building blocks.

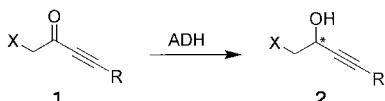
Our previous results provided evidence that in the reduction of propargylic ketones by oxidoreductases, one substituent of the substrate must not exceed a certain size.^[7] Most likely, this substituent has to be small enough to fit into a cavity of the active site of the enzyme. Therefore, we synthesized a number of alkynones with diverse steric demands, and determined the ability of various alcohol dehydrogenases to reduce these compounds. In a UV assay, we identified three alcohol dehydrogenases (ADHs) that accept propargylic substrates with substituents of the size of chloro- and bromomethyl groups (data not shown). α -Halogenated propargylic ketones **1**, which were easily synthesized in one step,^[8] were reduced by horse liver alcohol dehydrogenase (HLADH), *Thermoanaerobium brockii* ADH (TBADH), and *Lactobacillus brevis* ADH (LBADH) (Table 1). All these enzymes are commercially available.^[9] Additionally, two are efficiently overproduced in a recombinant *Escheria coli* strain (TEADH and recLBADH).^[10, 11] All these oxidoreductases reduce aromatic and aliphatic α -chloropropargylic ketones with high activity. α -Bromopropargylic ketones are also suitable substrates; however, the enzymatic

activity of TBADH and recLBADH decreases, probably as a result of steric interactions. Interestingly, this characteristic differs for HLADH. This enzyme generally prefers cyclic ketones, whereas aliphatic compounds are known to be poor substrates.^[12] Applying propargylic ketones, the α -halogenation increases the activity notably from nonhalogenated through chlorinated to brominated derivatives, thus making these compounds exceptional in the substrate range of HLADH.

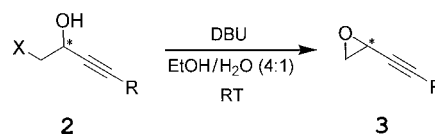
As a result of the low solubility of **1**, about 25 % of a short-chain alcohol was added, surprisingly without any significant loss of enzymatic activity of HLADH and recLBADH.^[13] Conveniently, as all the investigated ADHs recycle the cofactor NAD(P)⁺ by oxidation of the auxiliary alcohol, the addition of a second NAD(P)⁺-reducing enzyme was not necessary. The large excess of short-chain alcohol shifted the substrate/product equilibrium towards the desired propargylic alcohol **2**, thus resulting in almost quantitative conversions with high total turnover numbers (TTN) of the cofactor.^[14] Enzymatic reductions could be carried out on a preparative scale by using deionized water instead of buffer^[15] and were easily scaled up by using fed-batch technique. Thus, mmol quantities of substrate **1a** were converted by using as little as 0.005 mol % of cofactor, which corresponds to a TTN of 20000, and small amounts of recLBADH (~100 units enzyme g⁻¹ substrate).^[16] After a reaction time of 24–36 h, the pure product (NMR and GC analysis) was easily isolated by extraction without further purification in >95 % yield. HPLC analysis revealed >99 % conversion and, additionally, only one single enantiomer could be detected (*ee* >99 %).^[17] Currently, investigations into the reduction of 1-(chloro or bromo)-3-butyn-2-one are in progress. recLBADH converts these substrates into enantiopure *R* alcohols **2** (X = Cl, Br; R = H), thus resulting in an interesting switch of the enantioselectivity of the enzymatic reduction. As the enantiomers (*S*)-**2** (X = Cl, Br; R = H) can be obtained by recLBADH reduction of **1b–d** and subsequent removal of the silyl protecting group, this enzyme offers unique access to a pair of enantiomers.

Propargylic alcohols **2** can easily be converted in good yield into the corresponding epoxides **3** without racemization. Treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in EtOH/H₂O (4:1) at ambient temperature led to ring closure (Scheme 1). After workup by extraction, no further purification was necessary since by-products could not be detected. This general approach to enantiomerically pure terminal propargylic epoxides^[18] offers multifaceted applications in organic chemistry as has been shown, for instance, by Hiyama and co-workers in the synthesis of HMG-CoA reductase inhibitor NK-104.^[19] For this purpose, epoxide (*R*)-**3b** was obtained by ex-chiral pool synthesis in six steps and with an overall yield of 20 %.^[18a,b] Since terminal propargylic epoxides

Table 1. Relative enzymatic activities of HLADH, TBADH and recLBADH.

				
Alcohol		HLADH ^[a]	TBADH ^[a]	recLBADH ^[a]
		activity [%] ^[b] (configuration)		
2a	X = Cl R = Ph	32 (<i>R</i>)	53 (<i>R</i>)	70 (<i>S</i>)
2b	X = Cl R = TBS	24 (<i>R</i>)	51 (<i>R</i>)	37 (<i>S</i>)
2c	X = Cl R = TMS	15 (<i>R</i>)	74 (<i>R</i>)	28 (<i>S</i>)
2d	X = Br R = TMS	35 (<i>R</i>)	4 (<i>R</i>)	18 (<i>S</i>) ^[c]
2e ^[d]	X = H R = Ph	6 (<i>S</i>)	47 (<i>S</i>)	142 (<i>R</i>)

Assay conditions: substrate (2 mM), NAD(P)H (0.25 mM), MgCl₂ (1 mM), TEA/NaOH buffer (100 mM), pH = 7.0. [a] All alcohols have an enantiomeric excess of >99 % as determined by HPLC (**2a, e**) or GC (Mosher's ester of **2b–d**) on chiral stationary phase. The configuration of **2a** and **b** was determined by comparison of the optical rotation of the corresponding epoxide with literature data. The configuration of **2c, d** was determined with respect to mechanistic aspects of enzyme catalysis and by comparison of the NMR data of the corresponding *R* and *S* Mosher's ester. The configuration of **2e** was determined by comparison of the optical rotation with literature data. [b] The enzyme activity was determined by the decrease of the NAD(P)H extinction at 340 nm relative to the 100 % standard (HLADH: cyclohexanone; TBADH: 2-butanone; recLBADH: ethyl 5-oxohexanoate). [c] *ee* 98.5 %. [d] The change in configuration is because of the different CIP priorities. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl.



Scheme 1. Conversion of chlorohydrins **2** into epoxides **3**.

and chlorohydrins can be selectively modified at C1 or C2 at their particular functionalities as well as at C3 or C4 at the triple bond,^[20] these compounds are of great use in synthetic chemistry.

In conclusion, we have developed an efficient method to obtain halogenated propargylic alcohols **2** as well as terminal propargylic epoxides **3** with excellent enantiomeric excesses. The commercial availability and the easy handling of all components offers ready access to building blocks that were hardly known previously. The multifunctionality of these enantiopure C₄ units allows highly flexible synthetic transformations, thus making them interesting intermediates in the synthesis of natural compounds and drugs.

Experimental Section

(S)-2a: A solution of **1a** (1.56 g, 8.76 mmol) in 2-propanol (30 mL) was added over 20 h (25 $\mu\text{L min}^{-1}$) to a stirred solution of NADP⁺ (3.6 mg, 4.2 μmol ; 0.05 mol %), 2-propanol (30 mL) and recLBADH (150 U) in triethanolamine–HCl buffer (150 mL; 100 mM; 1 mM MgCl₂; pH 6.5) at room temperature. After stirring for an additional 28 h, deionized water (600 mL) was added, and the reaction mixture was extracted with CH₂Cl₂ (3 $\times$ 200 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give analytically pure (NMR, GC-MS) alcohol **(S)-2a** as a yellow oil (1.55 g, 8.60 mmol, 98% yield). > 99% ee;^[17] $[\alpha]_{\text{D}}^{20} = +25.4$ ($c = 1.4$, CHCl₃); ¹H NMR (300 MHz, CDCl₃): $\delta = 2.56$ (d, $J = 6.1$ Hz, 1H; OH), 3.76 (dd, $J = 11.1$, 6.5 Hz, 1H; CHCl), 3.83 (dd, $J = 11.1$, 4.1 Hz, 1H; CHCl), 4.84 (m, 1H; CH), 7.36 (m, 3H; ArH), 7.47 (m, 2H; ArH); ¹³C NMR (75.5 MHz, CDCl₃): $\delta = 49.3$ (C1), 63.2 (C2), 86.1, 86.6 (C3, C4), 122.0, 128.6, 129.1, 132.0 (ArC); HR-MS (EI): calcd for C₁₀H₉ClO: 180.0342, found: 180.0344.

(R)-2a: A solution of **1a** (1.56 g, 8.76 mmol) in ethanol (45 mL) was added over 2 h (15 mL h⁻¹) to a stirred solution of NAD⁺ (6.0 mg, 8.42 μmol ; 0.10 mol %), ethanol (75 mL), and HLADH (250 U) in triethanolamine–HCl buffer (500 mL, 100 mM; pH 7.0) at room temperature. After stirring for an additional 34 h, deionized water (1000 mL) was added and the reaction mixture was extracted with CH₂Cl₂ (3 $\times$ 300 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo to yield analytically pure (NMR, GC-MS) alcohol **(R)-2a** as a yellow oil (1.53 g, 8.50 mmol, 97%). > 99% ee;^[17] $[\alpha]_{\text{D}}^{20} = -25.2$ ($c = 1.3$, CHCl₃);^[17] ¹H NMR and ¹³C NMR: as for **(S)-2a**.

(R)-3a: Alcohol **(R)-2a** (588 mg, 3.3 mmol) was added to a solution of DBU (1.5 mL, 10.0 mmol) in EtOH/H₂O (20 mL, 4:1). The mixture was stirred for 90 min at room temperature, followed by addition of H₂O (100 mL) and extraction with ethyl acetate (3 $\times$ 30 mL). The organic layers were dried over Na₂SO₄ and concentrated in vacuo to yield analytically pure (NMR, GC-MS) epoxide **(R)-3a** as an orange oil (441 mg, 3.1 mmol, 93%). Purification by flash chromatography ('Iso-hexane'/ethyl acetate 30:1; 'Iso-hexane': Fluka 34969, mixture of isomers) yielded **(R)-3a** as a colorless oil (376 mg, 2.6 mmol, 80%) > 99% ee;^[21] $[\alpha]_{\text{D}}^{20} = -47.0$ ($c = 1.3$, acetone);^[18c] $[\alpha]_{\text{D}}^{20} = -42$ ($c = 2.0$, acetone 78% ee). ¹H NMR (300 MHz, CDCl₃): $\delta = 3.02$ (d, $J = 3.3$, 2H; CH₂), 3.60 (t, $J = 3.3$, 1H; CH), 7.34 (m, 3H; ArH), 7.47 (m, 2H; ArH); ¹³C NMR (75.5 MHz, CDCl₃): $\delta = 40.4$ (C2), 49.3 (C1), 83.6, 85.9 (C3, C4), 122.1, 128.5, 129.0, 132.1 (ArC).

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- [15] The use of deionized water requires pH monitoring and adjustment with aqueous NaOH. In contrast to HLADH and recLBADH, a decrease in enzymatic activity of TBADH in deionized water was observed. For simplification of the g-scale conversions with recLBADH and HLADH, these reactions were performed in aqueous buffer.
- [16] In a fed-batch optimized with respect to low amounts of cofactor, ketone **1a** (1.1 mmol) in deionized water (20 mL) and 2-propanol (8 mL) was quantitatively reduced as described in the experimental section by using NADP⁺ (0.055 μmol) and recLBADH (20 U).
- [17] Enantiomers of **2a** were separated by means of HPLC on a Chiralcel OB column (250 $\times$ 4 mm, equipped with a precolumn, 80 $\times$ 4 mm, Daicel Chem. Ind., 20°C, 0.5 mL min⁻¹, 'Iso-hexane'/2-propanol 95:5), $R_t = 39.0$ min ((S)-**2a**), 44.7 min ((R)-**2a**).

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- [20] Alcohols (*R*)- and (*S*)-**2a** were converted into the corresponding *E*- and *Z* allylic alcohols by using Red-Al or Lindlar catalyst, respectively. The olefinic products were obtained in high yield, without racemization (*ee* > 99 %) and excellent *E/Z* ratios (Red-Al: *E/Z* 100:0; Lindlar catalyst: *E/Z* 5:95). Thus, another class of hardly known highly functionalized synthetic intermediates is easily accessible; T. Schubert, M. Müller, unpublished results.
- [21] The *ee* values were determined by conversion of epoxide (*S*)-**3a** and rac-**3a** into the terminal nitrile, by treatment with a threefold excess of KCN in ethanol/water (4:1) at 50 °C for 4 h. The nitrile obtained was separated by means of HPLC on a Chiralcel OB column (20 °C, 0.5 mL min⁻¹, 'Iso-hexane'/2-propanol 95:5), *R*_t = 68.6 min ((*R*)-**3a**), 79.3 min ((*S*)-**3a**).

Titanium Silsesquioxanes Grafted on Three-Dimensionally Netted Polysiloxanes: Catalytic Ensembles for Epoxidation of Alkenes with Aqueous Hydrogen Peroxide**

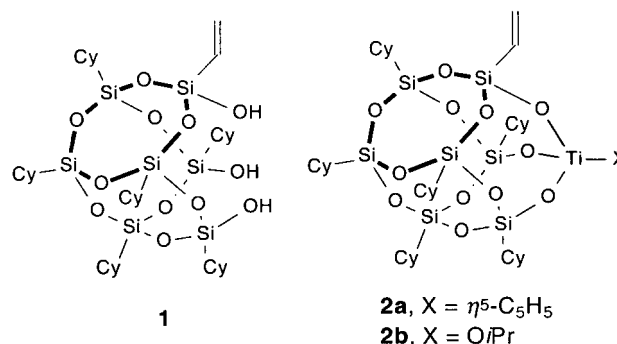
Maria D. Skowronska-Ptasinska,
Martinus L. W. Vorstenbosch, Rutger A. van Santen,
and Hendrikus C. L. Abbenhuis*

Few catalysts have been truly efficient in alkene epoxidation with aqueous hydrogen peroxide. Development of such catalysts is an important goal since with regard to desirability, this oxidant comes only second to oxygen itself.^[1] Currently, the best catalyst in this field is the synthetic titanium-containing zeolite, titanium silicalite-1 (TS-1),^[2] which is active for a wide range of oxidation reactions, including epoxidation.^[3] For TS-1, activity seems to originate from a combination of a robust active Ti(OSi≡)_n site (*n* = 3, 4),^[4] and its location in a hydrophobic channel or cavity in the MFI (ZSM-5) structure.^[5] The resulting catalytic ensemble prevents poisoning of the active site by water as well as unproductive decomposition of the oxidant. A series of titanium silsesquioxane complexes with structural elements that are very similar to the active TS-1 site have been reported to function as homogeneous catalysts.^[6] Although some of

these complexes are stable in aqueous media,^[7] none could perform alkene epoxidation with hydrogen peroxide. It is tempting to ascribe this to the lack of a combination of the active titanium site with a suitable hydrophobic environment. The same phenomenon can account for the lack of catalytic activity in a study by Sherrington and Alder on Ti^{IV}-grafted polysiloxane networks prepared from silanol-rich supports. These materials, showed no activity in alkene epoxidation with 30 % aqueous H₂O₂.^[8] This can be ascribed to either the presence of residual silanol groups that make the materials more hydrophilic thus rendering unsuitable catalytic ensembles or to the presence of Ti centers with inappropriate structures.

Herein, epoxidation catalysts are reported that, like TS-1, epoxidize 1-octene but also substrates that are too large for TS-1 such as cyclooctene and cyclododecene. In this approach, ensembles are made from robust titanium silsesquioxane complexes. These are grafted on commercially available linear methylhydrosiloxane–dimethylsiloxane copolymers and then cross-linked by reaction with vinyl-terminated polydimethylsiloxanes. The resulting titanium polysiloxane materials are hydrophobic, three-dimensionally netted polymers that enclose the titanium sites in cavities that can, in principle, be varied according to the choice of the starting materials. Since titanium polysiloxanes are found to epoxidize alkenes with aqueous hydrogen peroxide, while titanium silsesquioxane complexes alone do not have this ability, we demonstrate the need for catalytic ensembles in this area of science.

Vinyl silsesquioxane trisilanol [(H₂C=CH)(*c*-C₆H₁₁)₆-Si₇O₉(OH)₃] (**1**)^[9] can be easily converted to new titanium silsesquioxane complexes [(H₂C=CH)(*c*-C₆H₁₁)₆Si₇O₁₂TiX] (**2a**, X = η⁵-C₅H₅ (Cp), **2b**, X = OiPr) by reaction with [Cl₃TiCp] or [Ti(OiPr)₄], respectively. These reactions are



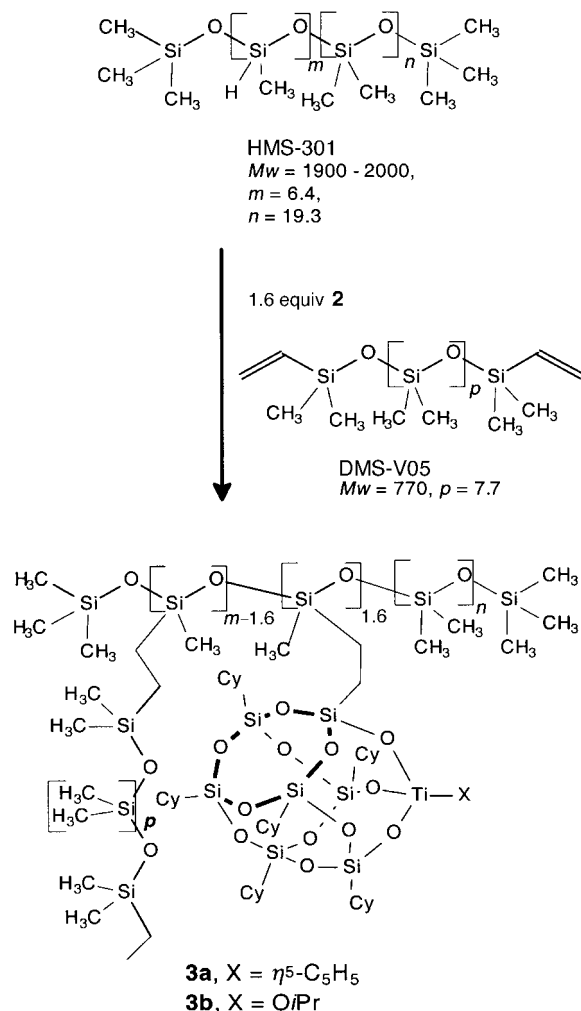
similar to those previously described for the related, unfunctionalized silsesquioxane trisilanol [(*c*-C₆H₁₁)₆Si₇O₉(OH)₃].^[6b, 10] For both new complexes, the ¹³C NMR spectra (400 MHz, CDCl₃) are particularly informative, showing four peaks for the cyclohexyl methine carbon atoms (ratio 2:1:1:2 for **2a** and 1:1:2:2 for **2b**) characteristic for C₂-symmetric, monomeric silsesquioxane titanium species. Attempts to obtain crystals of **2** suitable for X-ray analysis were unsuccessful thus far.

Vinyl-bearing metallosilsesquioxanes readily undergo platinum-catalyzed hydrosilylation,^[11] thus for the immobilization

[*] Dr. H. C. L. Abbenhuis, Dr. M. D. Skowronska-Ptasinska, M. L. W. Vorstenbosch, Prof. Dr. R. A. van Santen
Schuit Institute of Catalysis
Eindhoven University of Technology
P. O. Box 513, 5600 MB Eindhoven (The Netherlands)
Fax: (+31) 40-24-55-05-4
E-mail: H.C.L.Abbenhuis@chem.tue.nl

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of **2**, linear methylhydrosiloxane dimethylsiloxane copolymers were chosen as a support. These copolymers are commercially available over a wide range of molecular weight and reactive silane content. Both **2a** and **2b** can be smoothly grafted on these copolymers, followed by cross-linking with the vinyl-terminated polydimethylsiloxanes DMS-V05, also conveniently available (Scheme 1), to form brittle organosiliceous materials **3**.



Scheme 1. Synthesis of three-dimensionally netted polymeric catalysts **3**.

The first step of the hydrosilylation of **2** with the methylhydrosiloxane–dimethylsiloxane copolymer HMS-301 can be monitored by ^1H NMR and ^{13}C NMR spectroscopy. Already half an hour after addition of the Pt hydrosilylation catalyst (ppm amounts) to the reaction mixture of **2** and HMS-301 in deuterated benzene (at the concentrations applied for polymer preparation), resonances assignable to vinyl groups have disappeared in both ^1H NMR and ^{13}C NMR spectra, and simultaneous changes of the cyclohexyl methine carbon pattern of the silsesquioxanes have taken place as observed by ^{13}C NMR spectroscopy.

Catalytic activity of materials **3** was first studied in the epoxidation of cyclooctene with equimolar amounts of *tert*-butylhydroperoxide (TBHP, 1.8 M in isooctane, 0.33 mol % Ti,

50 °C). From these experiments, it is clear that only grafted titanium derivatives yield truly heterogeneous catalysts. After reaction times of 24 h, 73 and 55 % conversion of cyclooctene to cyclooctene epoxide was found for **3a** and **3b**, respectively, with >95 % selectivity. For comparison, a material **4b** related to **3b** resulting from a known, non-vinyl derivative [$(\text{C}_6\text{H}_{11})_7\text{Si}_7\text{O}_{12}\text{TiOiPr}$]^[6b] that is only physically “trapped” in the polysiloxane, was prepared by using the same polymerization procedure as for **3b**. For the system **4b**, using the same conditions as above, 61 % conversion of cyclooctene to cyclooctene epoxide was observed after 24 h. Hot filtration experiments, however, reveal that only materials **3** are truly heterogeneous catalysts, as the epoxidation stops when the polymer is filtered out of the reaction mixture. In the case of **4b** epoxidation proceeds further after filtration, due to leaching of [$(\text{C}_6\text{H}_{11})_7\text{Si}_7\text{O}_{12}\text{TiOiPr}$] from the polymer.

Materials **3** were subsequently tested in the catalytic epoxidation of neat cyclooctene with 35 % aqueous hydrogen peroxide ($\text{H}_2\text{O}_2/\text{alkene} = 1:4$, 0.33 mol % Ti, 50 °C); the results are presented in Figure 1. Epoxide yields are based on

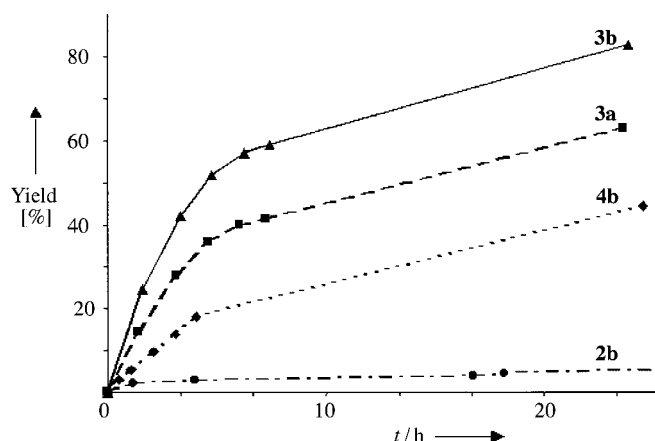


Figure 1. Heterogeneous epoxidation of cyclooctene with hydrogen peroxide catalyzed by **2–4**; epoxide yields are based on the amount of peroxide used.

the amount of peroxide used. From these experiments, it is clear that only grafted-titanium derivatives yield active catalysts in application with aqueous hydrogen peroxide. Material **4b** is less active than its fully heterogeneous analogue **3b**, despite having at least the same Ti content as **3b** (Figure 1). The lower catalytic activity of **4b** can be easily explained by leaching of [$(\text{C}_6\text{H}_{11})_7\text{Si}_7\text{O}_{12}\text{TiOiPr}$] from the polymer, the unsupported complex being inactive in epoxidation with H_2O_2 .

The reaction scope of the most active catalyst **3b** was found to cover *n*-alkenes and large cyclic alkenes. For cyclododecene ($\text{H}_2\text{O}_2/\text{alkene} = 1:4$, 0.33 mol % Ti, 50 °C) a maximum epoxide yield of 45 % was reached; the remaining portion of the peroxide decomposed unproductively to O_2 . Catalytic epoxidation with **3b** of 1-octene was optimized to give the epoxide in 62 % yield in 1.5 h ($\text{H}_2\text{O}_2/\text{alkene} = 1:12$, 2 mol % Ti, 80 °C); this is equivalent to a turnover frequency of about 20 h^{-1} . Reported turnover frequencies for 1-octene epoxidation by TS-1 vary from 4 to about 80 h^{-1} and generally increase

significantly with increasing alkene/H₂O₂ ratios.^[12] This is also valid for our systems. Since the synthesis of catalysts **3** allows an interesting degree of freedom with regard to support properties, such as tether length and the nature of the immobilized silsesquioxane complex, more active catalysts may result from further optimization. Such work is currently in progress together with comparative experiments using EURO TS-1.^[12]

The results presented demonstrate that grafting of functionalized titanium silsesquioxanes on polysiloxanes provides a way to realize the formation of a catalytic ensemble that is capable of performing epoxidation with aqueous hydrogen peroxide. Clearly, the entire system is capable of outperforming the sum of its parts; it is the synergy between active site and its environment that allows the catalysts presented here, and likewise TS-1, or even metalloenzymes^[13] to achieve their desirable performances.

Experimental Section

Synthesis of [(H₂C=CH)(c-C₆H₁₁)₆Si₇O₁₂TiCp] (**2a**): [CpTiCl₃] (0.658 g) was added to [(H₂C=CH)(c-C₆H₁₁)₆Si₇O₉(OH)₃] (2.75 g, 3.00 mmol) in toluene (35 mL). Then an excess of dry pyridine (1.5 mL) was added to the mixture, which was stirred for 1 h at room temperature, filtered, and the filtrate was concentrated to about 10 mL. After addition of acetonitrile (10 mL), **2a** (2.35 g, 76% yield) was isolated as white crystals. ¹H NMR (CDCl₃, 400 MHz): δ = 6.53 (s, 5H; C₅H₅), 6.0 (m, 3H; CH₂=CH-), 1.75 (m, 30H; CH₂-C₆H₁₁), 1.26 (m, 30H; CH₂-C₆H₁₁), 0.76 (m, 6H; CH-C₆H₁₁); ¹³C NMR (CDCl₃): δ = 134.89 (CH₂-vinyl), 130.97 (s, CH-vinyl), 116.26 (s, CH-Cp), 27.64, 27.57, 27.55, 27.52, 27.11, 27.01, 26.93, 26.89, 26.83, 26.77, 26.65 (s, CH₂-C₆H₁₁), 23.43, 23.22, 23.20, 23.15 (s, CH-C₆H₁₁, ratio 2:1:1:2); ²⁹Si NMR (CDCl₃): δ = -66.14, -68.69, -69.33, -69.52 (s, Si-CH, 2:1:2:1 ratio), 78.01 (s, Si-vinyl); elemental analysis calcd (%) for C₄₃H₇₄O₁₂Si₇Ti: C 50.26, H 7.26; found: C 50.19, H 7.37.

Synthesis of [(H₂C=CH)(c-C₆H₁₁)₆Si₇O₁₂TiOiPr] (**2b**): [Ti(OiPr)₄] (0.91 mL, 3.00 mmol) was added to [(H₂C=CH)(c-C₆H₁₁)₆Si₇O₉(OH)₃] (2.75 g, 3.00 mmol) in hexane (25 mL). The mixture was stirred at 50 °C for 1.5 h and the solvent was evaporated in vacuo to yield **2b** (3.03 g) as a crude white powder. ¹H NMR (CDCl₃, 400 MHz): δ = 6.06 (m, 2H; CH₂=), 5.89 (m, 1H; CH=), 4.62 (m, 1H; CH(CH₃)₂), 1.77 (br m, 30H; CH₂-C₆H₁₁), 1.27 (m, 36H; CH₂-C₆H₁₁ and CH₃-OiPr), 0.81 (m, 6H; CH-C₆H₁₁); ¹³C NMR (CDCl₃): δ = 135.69 (s, CH₂-vinyl), 130.03 (s, CH-vinyl), 79.51 (s, CH(CH₃)₂), 27.52, 26.88, 26.83, 26.75, 26.70, 26.66 (s, CH₂), 25.65 (s, CH₃, OiPr), 23.22, 23.19, 23.14, 23.09 (s, CH, 1:1:2:2 ratio); ²⁹Si NMR (CDCl₃): δ = -67.20, -68.60, -69.36, -69.53 (s, Si-CH, 2:1:2:1 ratio), -78.96 (s, Si-vinyl); elemental analysis calcd for C₄₁H₇₆O₁₃Si₇Ti: C 48.21, H 7.50; found: C 49.05, H 7.82.

Immobilization of **2a** and **2b** in polysiloxane (**3**): Compound **1a** (726.9 mg) dissolved in toluene (3 mL) was added to methylhydrosiloxane–dimethylsiloxane copolymer (3.0 g; HMS-301, Gelest) diluted with toluene (4 mL) and platinum divinyltetramethyldisiloxane complex in xylene (20 mg; Gelest). The mixture was stirred at room temperature for 0.5 h, and then the Pt catalyst (20 mg) and vinyl-terminated polydimethylsiloxane DMS-V05 (2.40 g) diluted in hexane (3 mL) was added. The reaction

mixture was stirred for additional 15 min, poured into a Petri plate to evaporate the solvent and cured at 80 °C overnight. The brittle polymer was ground, and continuously extracted with diethyl ether for two days to remove ungrafted titanium. After filtration and drying polymer **3a** (5.1 g) was obtained. Elemental analysis: calcd: Ti 5.5; found: Ti 5.1 mg g⁻¹. The same procedure was applied using **2b** (720 mg) to achieve the same initial Ti content (5.5 mg Ti g⁻¹ of reacting components) to give the polymer **3b** (4.8 g).

Alkene epoxidation: The epoxidation tests were carried out in 2 mL stirred batch reactors by using **3** (ca. 60 mg). For epoxidation with TBHP, TBHP (1.8 mmol) and cyclooctene (1.8 mmol) in isooctane were used. Epoxidation with aqueous H₂O₂ was carried out using H₂O₂ (35% aqueous solution) and neat alkene in the molecular ratios specified above. Excess of alkene is used here to suppress unproductive decomposition of H₂O₂ to O₂. Samples taken from the reaction mixtures were analyzed by GC analysis using a Carlo Erba GC6000 Vega Series apparatus equipped with a capillary DB-1 column and a FID (flame ionisation detector). For this purpose all samples contained 1,3,5-trimethylbenzene (25 µL; >98%, Merck) as GC internal standard. Epoxide yields are based on the amount of peroxide used.

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Designing Protein Denaturants: Synthetic Agents Induce Cytochrome *c* Unfolding at Low Concentrations and Stoichiometries**

Rishi K. Jain and Andrew D. Hamilton*

In contrast to active site inhibitors, very little attention has been given to the design of molecules that alter protein function by changing the native conformation of the target. Such “conformational drugs” could act by returning a misfolded (or mutant) protein to its native state, thereby leading to a gain of function (as has been demonstrated recently with mutated p53^[1]), or by inducing a conformational change in an active protein with consequent loss of function.^[2] An extreme example of the second case would be a molecule that, on binding to a noncatalytic region of the protein, would force an unraveling of its tertiary and secondary structure.^[3] To be effective, such a denaturant should act selectively at near stoichiometric levels and at physiological (micromolar or lower) concentrations.^[4, 5] Herein, we describe a class of synthetic ligands that function in this way by binding tightly to and dramatically lowering the melting temperature of cytochrome *c*, a protein commonly used in unfolding studies.

At physiological pH, cytochrome *c* (cyt. *c*), in common with most proteins, requires molar concentrations of guanidinium chloride or urea for denaturation. Lower concentrations of certain phospholipids^[6] and surfactants^[7] can be effective in destabilizing cyt. *c* but usually at a large excess relative to the protein and at concentrations close to or above their critical micellar concentration (c.m.c.). That stoichiometric unfolding of cyt. *c* might be possible is suggested by the thermodynamic consequences of its binding to cytochrome *c* peroxidase^[8] and cytochrome oxidase.^[9] Both of these proteins bind tightly to cyt. *c* through complementary protein–protein interactions and cause a 20–27 K decrease in its melting temperature. Thus, a synthetic molecule that matches the distribution of charged and hydrophobic residues on a surface region of cyt. *c* might mimic the function of the natural protein partners and lower the temperature at which it denatures.

The principal protein–protein interaction site on cyt. *c* involves a hydrophobic patch near the heme edge region that is surrounded by several lysine residues (Figure 1 a).^[10] Compound **1** (Scheme 1), containing four anionic Tyr–Asp substituents around a central porphyrin ring, provides a good match for this distribution of functionality and binds tightly to the heme edge region of cyt. *c* ($K_d = 20$ nM).^[11] Moreover, CD studies at room temperature indicated that binding of **1** leads to no detectable change in the secondary structure of the cyt. *c*. However, the thermal stability of the protein is dramatically affected. At pH 7.4, cyt. *c* (at 10 μ M) shows a melting temperature (T_m) of 85 °C, as monitored by the loss of

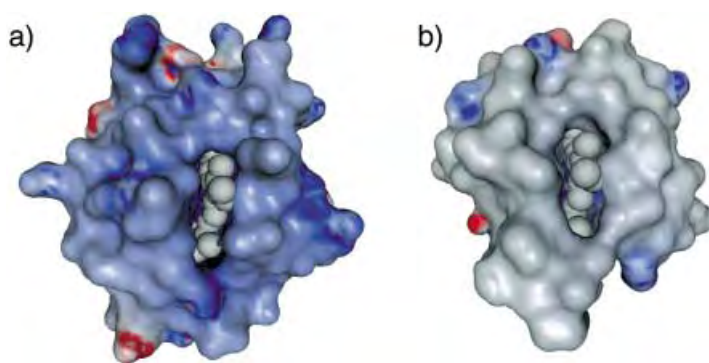
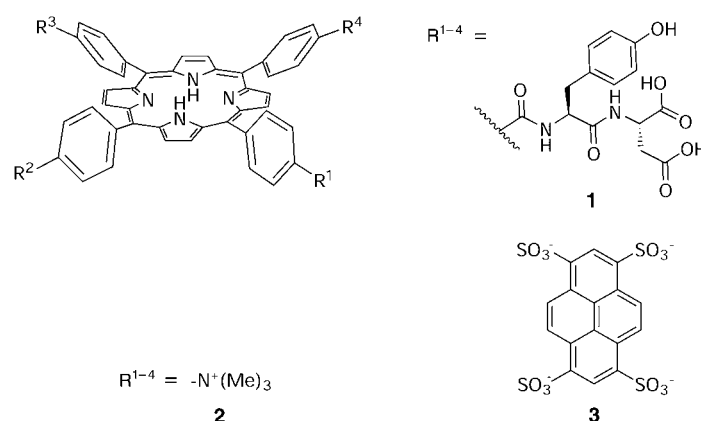


Figure 1. a) X-ray crystal structure of horse cyt. *c*, and b) *Pseudomonas aeruginosa* cyt. c551 viewed towards the heme edge region and displayed as surface models color coded by electrostatic (red negative, blue positive) surface potential.



Scheme 1. Chemical formulas of compounds **1–3** employed in the denaturation studies.

the CD signal at 222 nm (Figure 2). Upon addition of 1.2 equivalents of **1**, the T_m dropped to 64 °C. Increasing the concentration of **1** to 60 μ M (6 equiv) lead to a further decrease in T_m to 53 °C, corresponding to a 32 K reduction relative to the unbound protein. A single equivalent of **1**, however, is all that is needed to achieve this effect. At 70 °C, titration of **1** into a 10 μ M solution of cyt. *c* leads to complete denaturation of the protein at 10 μ M (Figure 3).

Extending the thermal denaturation to 100 °C resulted in poor thermodynamic reversibility of cyt. *c* (~40 %) due to irreversible aggregation and misligation of heme.^[12] However, the lower temperatures required for the thermal transition of cyt. *c* in the presence of **1** lead to higher levels of reversibility (~90 %). If the irreversible step, according to the Lumry–Eyring model,^[13] proceeds at significant rates only at temperatures above the T_m , then the application of equilibrium thermodynamics will not lead to large errors.^[14, 15] Thus, the $\Delta\Delta G$ value, based on the decrease in T_m (21 K) when compound **1** is present at 1.2 equivalents, is approximately 5 kcal mol^{–1}.

The importance of matching protein surface features with recognition sites on the synthetic agent was emphasized by molecules with modified charge or hydrophobic characteristics. For example, tetrakis-*p*-trimethylaminophenylporphyrine, tetratosylate **2**^[16] is charge-mismatched relative to

[*] Prof. A. D. Hamilton, R. K. Jain
Department of Chemistry
Yale University
P.O. Box 208107, New Haven, CT 06520-8107 (USA)
Fax: (+1) 203-432-3221
E-mail: andrew.hamilton@yale.edu

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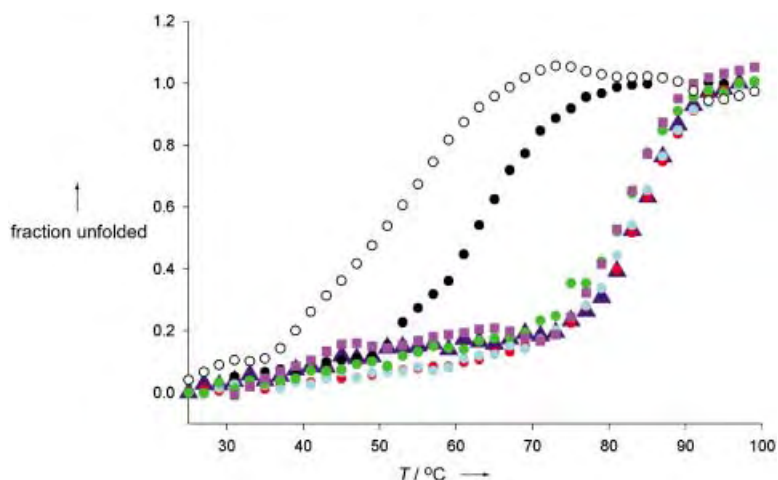


Figure 2. CD-monitored thermal denaturation profiles (θ at 222 nm). $\blacktriangle$ = cyt. *c* (10 μ M); $\bullet$ = cyt. *c* + **1** (10 μ M + 12 μ M); $\circ$ = cyt. *c* + **1** (10 μ M + 60 μ M); $\bullet$ = cyt. *c* + **3** (10 μ M + 12 μ M); $\bullet$ = cyt. *c* + **3** (10 μ M + 60 μ M); $\bullet$ = cyt. *c* + SDS (10 μ M + 12 μ M); $\blacksquare$ = cyt. *c* + SDS (10 μ M + 120 μ M). All experiments were carried out in a sodium phosphate buffer (5 mM, pH 7.4).

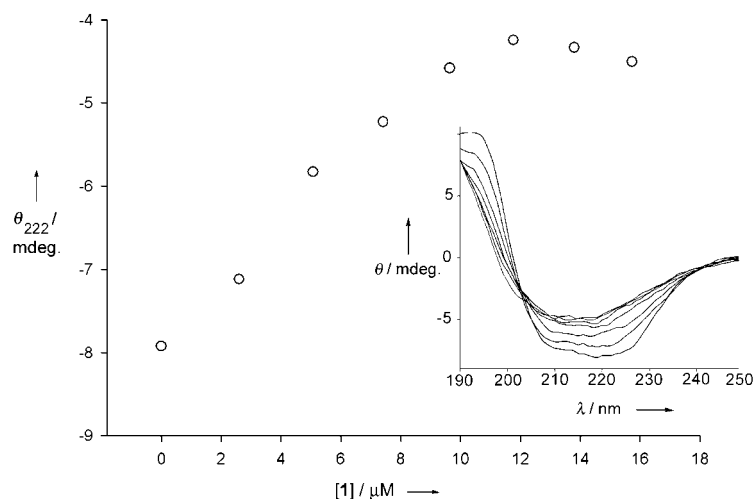


Figure 3. CD-monitored thermal denaturation profiles (θ_{222}) of cyt. *c* (10 μ M) as a function of added **1** at 70 °C. Inset: Far-UV CD spectrum (190–250 nm) of cyt. *c* at increasing concentrations of **1**. All experiments were carried out in a sodium phosphate buffer (5 mM, pH 7.4).

cytochrome *c* and shows no effect on its T_m even at 60 μ M concentrations (not shown). Tetrasulfonatopyrene tetra-sodium salt **3** serves as an anionic non-porphyrinoid compound, with appreciable hydrophobic surface area and binds moderately to cyt. *c* ($K_d = 8 \mu$ M) but has almost no effect on its thermal denaturation profile (Figure 2). The destabilizing influence of **1** on cyt. *c* is not due to nonspecific surfactant effects. At concentrations between 12 to 120 μ M, sodium dodecyl sulfate (SDS) did not affect the T_m of the protein (Figure 2). Previous reports have shown that SDS can denature cyt. *c* but at higher concentrations, close to the c.m.c. value of 2.3 mM.^[7] The UV absorption of **1** follows Beer's law, and no large aggregate formation was detected by resonance light scattering, indicating that the denaturing effect is due to discrete porphyrin monomers.

The importance of electrostatics in the denaturing effects of **1** was probed by studying proteins structurally related to native horse-heart cytochrome *c*. A modified cyt. *c*, where 60% of the lysine ϵ -amino groups are acetylated, has a very different surface charge distribution from the native protein but maintains a similar level of secondary structure at pH 7.4 and 25 °C albeit with a lower melting temperature (65 °C).^[17] Compound **1** binds much more weakly to acetylated cytochrome *c* ($K_d > 50 \mu$ M from fluorescence titration) and causes no change in its denaturation profile (Figure 4). These results point to an important role for the lysine residues in cyt. *c* for both the strong binding and destabilizing effects of **1**. Finally, we studied the effect of **1** on cytochrome *c*551 from *P. aeruginosa*^[18] (also known as cyt. *c*8) that has a similar structure to horse cyt. *c* but lacks the extensive cationic patch around the heme crevice (Figure 1b). The affinity of **1** for cyt. *c*551 ($K_d = 20 \mu$ M) was 10³ fold weaker than horse cyt. *c*, again pointing to a key role for the clustered lysine residues. However, the T_m from the thermal denaturation of cyt. *c*551 (82 °C) closely resembles that of horse cyt. *c* and showed no change (Figure 4) on addition of **1** (12 μ M). The lack of any effect on a closely related protein points to a degree of specificity in the action of **1** as a denaturant imposed by the matching of recognition surfaces.

The exact origin of this denaturing effect remains to be determined; however, tight binding of the denaturant to the native conformation of cyt. *c* seems to be a requirement. But how does that lead to unfolding of the protein? Charged amino acid residues on the surface of cyt. *c* (and many other proteins) are known to stabilize the native conformation.^[19] Charge optimization is believed to be a general mechanism for stability enhancement amongst thermophiles^[20, 21] and more recently has been applied to engineering highly thermostable proteins from mesophilic proteins.^[22, 23]

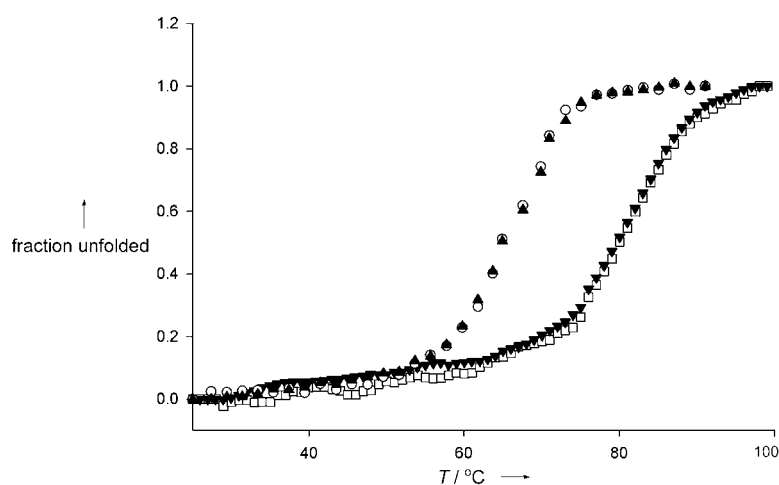


Figure 4. CD-monitored thermal denaturation profiles (θ_{222}). $\square$ = *P. aeruginosa* cyt. *c* (10 μ M); $\blacktriangledown$ = *P. aeruginosa* cyt. *c* + **1** (10 μ M + 12 μ M); $\circ$ = acetylated horse cyt. *c* (10 μ M); $\blacktriangle$ = acetylated horse cytochrome *c* + **1** (10 μ M + 12 μ M). All experiments were carried out at pH 7.4, 5 mM sodium phosphate buffer.



Horse cyt. *c* is a highly basic protein with a pI close to 10, where the charge state of the protein at pH 7 is +8. Association of **1**, an octaanionic species near neutral pH, leads to a major disruption of the coulombic interactions between the surface lysine residues and other regions of the protein with likely destabilization of the folded structure. In a related way, partial acetylation of the lysine (see above)^[17] and binding to acidic lipid membranes^[24] leads to a disruption of electrostatic surface potential and a similar destabilization of cyt. *c*. However, interaction with the denatured state may make an equally significant contribution to the effect of **1**.^[25, 26] In order to probe the interaction of **1** with the denatured state, we carried out a fluorescence quenching titration at higher temperatures. At 75 °C, the fluorescence of **1** is completely quenched by addition of approximately 0.33 equivalents of cyt. *c*. This indicates binding of at least 3 equivalents of **1** to the unfolded form of the protein, which would be expected to have a larger accessible hydrophobic surface area than the native conformation.^[27]

Compound **1** takes advantage of complementary hydrophobic and electrostatic interactions to achieve high affinity and selectivity. Like other destabilizers,^[5] **1** appears to act through destabilization of the native state in addition to the stabilization of the unfolded state. However, in the case of **1**, increased selectivity and efficacy is achieved through strong affinity to both states, inducing unfolding at much lower concentrations. This strategy offers a potentially general approach to designing molecules that denature other globular proteins with potency and selectivity.

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Synthesis and Characterization of Ag₂NiO₂ Showing an Uncommon Charge Distribution**

Martin Schreyer and Martin Jansen*

The unique structural features of silver-rich silver(I) oxides were the earliest experimental evidence suggesting attractive d¹⁰–d¹⁰ interactions between monovalent silver atoms.^[1, 2] In spite of bearing equal positive charges, the silver atoms in these compounds interconnect forming cluster-like ensembles corresponding to sections of the element structure of silver. Those structural features are accompanied by the formation of an empty band of mainly Ag-5s character near the Fermi level, capable of accommodating additional electrons. Consequently, silver is expected to adopt subvalent valence states in solid materials.^[3] Only a few examples such as, Ag₂F,^[4] Ag₃O,^[5] Ag₅SiO₄,^[6, 7] Ag₅GeO₄,^[6, 8] and Ag₅Pb₂O₆^[9] have been prepared to date. The properties range from metallic behavior in Ag₂F, Ag₃O, and Ag₅Pb₂O₆ to semiconducting in Ag₅SiO₄ and Ag₅GeO₄.

Surprisingly, the new silveroxonickelate Ag₂NiO₂ also contains subvalent silver. Conventionally, the oxidation states +1 and +2 would be assigned to silver and nickel, respectively, which correspond to the valence distribution in the homologous compound Ag₂PdO₂.^[10] These assignments, however, severely conflict with the structural features, magnetic moment, and spectroscopic properties found in Ag₂NiO₂. Instead, all the experimental findings are consistent with a charge distribution of [Ag₂]⁺[NiO₂][–].

Ag₂NiO₂ has been prepared by the solid-state reaction of Ag₂O and NiO under high oxygen pressure. Ag₂NiO₂ is a lustrous black solid and insensitive to air and water. The crystal structure has been determined and refined from X-ray and neutron powder data, and from single-crystal X-ray data.^[11] There are striking similarities with the delafossite structure^[12] on the one hand as well as with the silver suboxide Ag₃O^[5] and the silver subfluoride Ag₂F^[4] on the other.

[*] Prof. Dr. M. Jansen, Dr. M. Schreyer
Max-Planck-Institut für Festkörperforschung
Heisenbergstrasse 1
70569 Stuttgart (Germany)
Fax: (+49) 711-689-1502
E-mail: M.Jansen@fkf.mpg.de

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Figure 1 compares the structure of Ag_2NiO_2 with the structure of the delafossite AgNiO_2 ^[13] and silver subfluoride. In delafossites of the composition AgMO_2 (M = trivalent transition metal ion),^[12] MO_6 octahedra are linked by their edges to form cadmium chloride analogous layers. These layers are interconnected by linear O-Ag-O bridges and stacked along

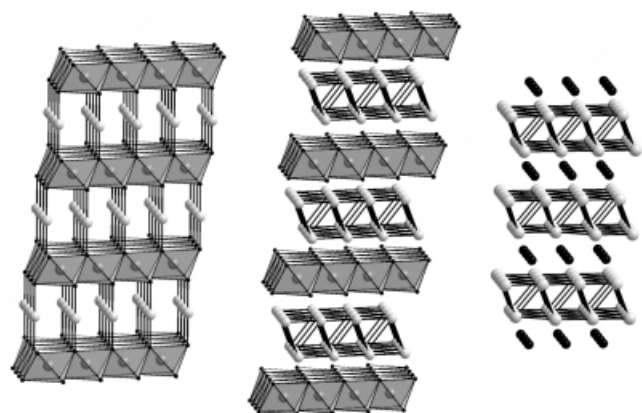


Figure 1. Comparison of the crystal structures of AgNiO_2 (left), Ag_2NiO_2 (center), and Ag_2F (right); silver: white, nickel: dark gray, fluorine: black.

the c axis (Figure 1) giving either the H- or R-polytype of the delafossite structure. Like AgNiO_2 , which represents the R-polytype, Ag_2NiO_2 also crystallizes in the trigonal space group $R\bar{3}2/m$ (No. 166). Compared to AgNiO_2 the a axis is slightly reduced from 2.9390(1) to 2.926(1) Å while the c axis is considerably elongated from 18.3700(1) to 24.0888(2) Å. The geometry of the cadmium-chloride-like NiO_2 layers remains virtually unchanged in Ag_2NiO_2 (Table 1). However,

Table 1. Distances [Å] and angles [°] in Ag_2NiO_2 and, for comparison, in AgNiO_2 ,^[13] Ag_2F ,^[4] and Ag_3O .^[5]

	Ag_2NiO_2	AgNiO_2 ^[13]	Ag_2F ^[4]	Ag_3O ^[5]
Ni-O	1.976(1)($\times 6$)	1.94($\times 6$)	–	–
Ag-O/Ag-F	2.506(1)($\times 3$)	2.12($\times 2$)	2.451($\times 3$)	2.292(1)
Ag-Ag in plane	2.926(1)($\times 6$)	2.939($\times 6$)	2.996($\times 6$)	3.074(1) ^[a]
Ag-Ag vertical	2.836(1)($\times 3$)	–	2.814($\times 3$)	2.833(1) ^[a]
O-Ni-O (1)	95.53(1)	98.50	–	–
O-Ni-O (2)	84.47(1)	81.50	–	–

[a] Mean distances.

the NiO_2 slabs are now separated by two staggered hexagonal silver layers. Thus, silver is coordinated by three oxygen atoms forming the basis of a trigonal pyramid with the silver atom at its top. This feature corresponds to the silver substructure of Ag_2F where the silver atoms also form layers of edge-sharing octahedra. As shown in Table 1, silver-silver and silver-anion distances are in good agreement with those in the silver subfluoride. Thus, $[\text{Ag}_2]^+$ and $[\text{NiO}_2]^-$ slabs alternate with each other, to form the structure of Ag_2NiO_2 . The in-plane silver-silver distances are 2.926(1) Å and thus similar to those in elementary silver (2.889 Å). The smallest distances between adjacent silver atoms of subsequent layers are even shorter at 2.836(1) Å. Since this short distance is not enforced by structural constraints, it must be directly attributed to chemical bonds between the silver atoms. This proposal

suggests that in Ag_2NiO_2 there is classic metallic Ag-Ag bonding mediated by an additional valence electron per two silver atoms, in addition to the d^{10} - d^{10} interactions effective in the R-delafossites. As there is only one crystallographic silver position and silver has an oxidation state of +1/2, at least partial metallic character can be attributed to this bond. Once again this is supported by the comparison with silver subfluoride Ag_2F and Ag_3O silver suboxide which are both metallic conductors.

These assignments of valence states are conclusively confirmed by the physical and spectroscopic properties of Ag_2NiO_2 . First, Ag_2NiO_2 is a good metallic conductor with a specific resistance of $2.18 \times 10^{-4} \Omega \text{ cm}$ at 298 K and a positive temperature coefficient (Figure 2) of $70.78 \mu\Omega \text{ cm K}^{-1}$. This

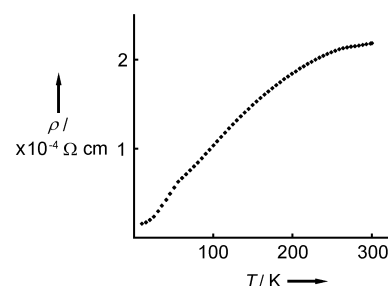


Figure 2. Temperature dependence of the electrical resistivity of Ag_2NiO_2 .

situation is comparable to the electric transport properties of Ag_2F and Ag_3O . Second, Ag_2NiO_2 is an antiferromagnet with $T_N = 56 \text{ K}$ and a Weiss temperature of 32 K (Figure 3). The magnetic moment as derived from the susceptibility data of the paramagnetic Curie-Weiss region above 56 K amounts to $\mu = 1.95 \mu_B$, which corresponds to Ni^{3+} center in a low spin state. At 250 K a slight baseline shift in the inverse magnetic susceptibility is observed that may be attributed to a change in the itinerant valence-electron concentration. However, a conclusive explanation of this latter features requires further investigation.

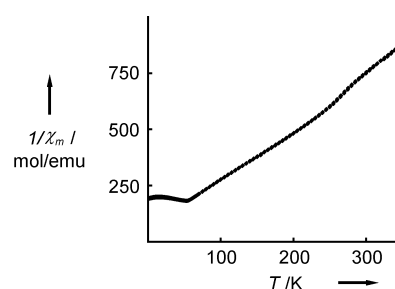


Figure 3. Temperature characteristic of the inverse molar susceptibility of Ag_2NiO_2 .

The valence states of silver and nickel were experimentally investigated by XANES-spectroscopy (Figure 4). With an increasing nickel oxidation state, the absorption edge is shifted to higher energies. Particularly, the absorption edges of Ag_2NiO_2 and AgNiO_2 coincide largely with respect to shape, turning points and band positions which indicates equal valence states for nickel in both compounds. Also, a compar-

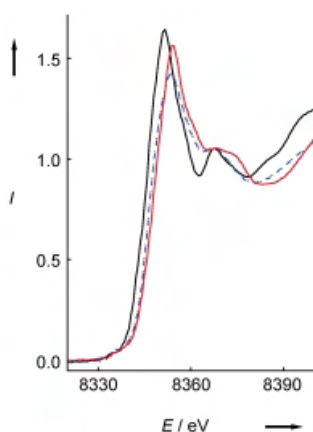


Figure 4. Ni-K-Edge-XANES-Spectra of Ag_2NiO_2 (blue broken line), AgNiO_2 (red solid line), and NiO (black solid line).

ison of the Ag-L₃-XANES-spectra of Ag_2O , AgNiO_2 , and Ag_2NiO_2 (Figure 5), lends strong support to the valence distribution suggested for Ag_2NiO_2 . Two different features of the spectra are to be considered. Firstly, the position of the absorption edge is related to the binding energy of the silver L-shell electrons which is expected to diminish with decreasing silver oxidation state. In Ag_2NiO_2 the absorption edge is significantly shifted to lower energy in comparison to Ag_2O and AgNiO_2 . This can be stated although the true position of the absorption edges in the latter two compounds is obscured by

the pre-edge absorption edge, an effect that increasingly shifts the absorption edge to lower energies. Secondly, the peak areas below the pre-edge absorption peaks correlate with the number of empty d-band states. These empty states are of significant magnitude for AgNiO_2 and Ag_2O and are virtually completely filled for Ag_2NiO_2 .^[14]

The peculiar valence-state distribution in Ag_2NiO_2 can be interpreted in terms of a stronger ligand-field stabilization of low-spin Ni^{3+} compared to Ni^{2+} centers in octahedral coordination and of low-lying silver 5s and 5p bands capable of accommodating excess electron density. The density of states (DOS) obtained for Ag_2F and Ag_2NiO_2 at the Hartree–Fock (HF) level show similar characteristics (Figure 6). Those parts of the DOS projected onto the 4d orbitals of silver are situated well below the Fermi level. The same is true for Ni-3d and O-3p contributions. The

energy range around the Fermi level is characterized by the presence of rather dispersed bands which predominantly correspond to Ag-5s/5p states. In this respect, the DOS and their projections in Ag_2NiO_2 closely resemble those in Ag_2F .

All current experimental and theoretical evidence leads to the conclusion that the new ternary silveroxonickelate Ag_2NiO_2 has an unexpected and unprecedented charge distribution. In particular, the presence of subvalent silver ($\text{Ag}^{1/2+}$) next to rather highly oxidized nickel (Ni^{3+}) center appears puzzling and resembles a short-circuited solid-state battery.

Experimental Section

Ag_2NiO_2 was formed by a solid-state reaction from a ground mixture of Ag_2O and NiO in the molar proportion 1.05:1 by annealing at 823 K under an oxygen pressure of 65 MPa. A potassium hydroxide solution (1.5 mL; 5 M) was added as a mineralizator, the reaction time was 24 h.

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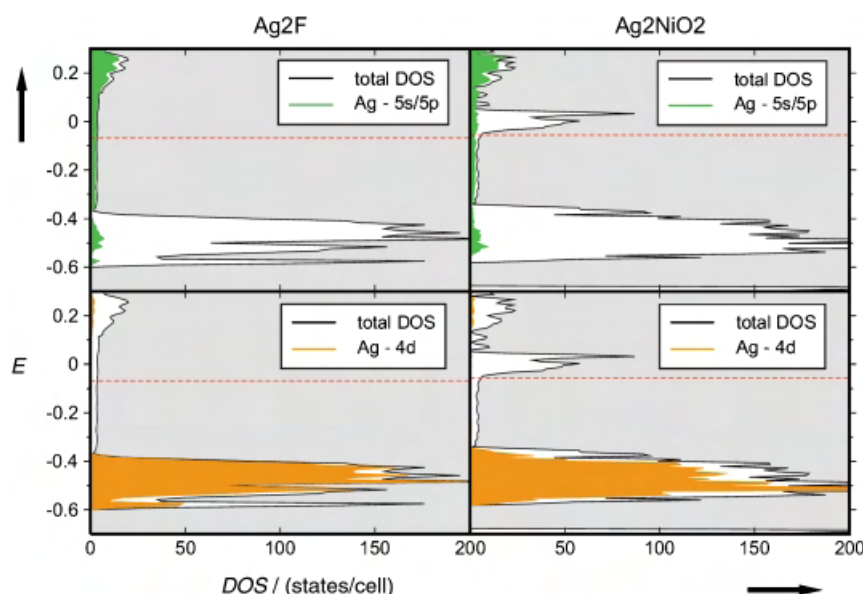


Figure 6. Comparison of the HF-calculated DOS of Ag_2F and Ag_2NiO_2 .

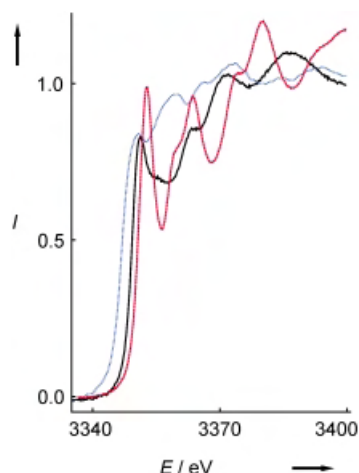


Figure 5. Ag-L₃-edge-XANES spectra of Ag_2NiO_2 (blue broken line), AgNiO_2 (red solid line), and (black solid line) Ag_2O .

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temperature coefficients, Rietveld refinement: R_{wp} : 0.0849, R_{bragg} : 0.0435, GOF: 3.585. Neutron diffraction data: Space group $R\bar{3}m$, $a = 2.92471(2)$, $b = 24.0746(4)$ Å, $V = 178.342(3)$ Å³, $Z = 3$; ROTAX/ISIS, Vanadium tube, time-of-flight (TOF) measurement, 3 detector banks; detector bank A: 1355 data points; detector bank B: 2129 data points; detector bank C: 2016 data points, 1006 observed reflections, 2 refined atomic parameters, 3 refined temperature coefficients, Rietveld refinement: $R_{wp} = 0.0283$, $\chi^2 = 3.619$. Single-crystal X-ray refinement: Space group $R\bar{3}m$, $a = 2.9193(4)$, $b = 24.031(4)$ Å, $V = 177.36(5)$ Å³, $Z = 3$; Bruker AXS Smart CCD 1000, MoK α , measurement range: $2.54^\circ < \theta < 34.49^\circ$, 131 reflections, refinement with SHELXL 97-2: $R_1 = 0.0132$, $R_{wp} = 0.0126$. 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-412279.

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A Mass Spectrometry Based Direct-Binding Assay for Screening Binding Partners of Proteins**

Hanfa Zou,* Qingchun Zhang, Zhong Guo, Baochuan Guo, Qiang Zhang, and Xiaoming Chen

Recent advances in genomics and proteomics have enabled the discovery of more drug targets than ever before. The majority of these drug targets are proteins. One of the most challenging areas of drug development is the search for novel receptor–ligand pairs and enzyme inhibitors,^[1, 2] as many novel proteins have no known binding partners. During the drug discovery process, the binding partners of a receptor or protein must be found in order to determine possible ways to address its pathological pathway.

Ligand fishing is a widely used process in which proteins are screened against a multitude of compounds to search for the binding partners of the proteins. The most common methods for ligand fishing are those based on direct binding and one of the most versatile direct-binding assays involves the use of biosensors based on surface plasma resonance (SPR).^[3–5] However, a major drawback of SPR is that once a sample is

identified as having a possible binding partner, other conventional biochemical techniques, for example, HPLC and mass spectrometry,^[6] need to be applied to identify the new ligand.

Herein we describe a novel on-probe direct-binding assay to screen the binding partners of a target protein. Contrary to the case in SPR, the captured binding partners in this direct-binding assay are directly analyzed on-probe by means of mass spectrometry. The target protein is first immobilized on a porous silicon probe. A sample that contains possible binding partners is then incubated with the probe, and the binding partners are captured by the immobilized protein. The captured binding partner is then identified by means of on-probe laser desorption/ionization time-of-flight (TOF) mass spectrometric analysis.

Unlike other mass spectrometry based assays in which biologically active probes are used for rapid analyses of a sample,^[7–12] this new assay involves desorption/ionization on silicon (DIOS)^[13–15] instead of matrix-assisted laser desorption/ionization (MALDI) in the ionization process. The use of DIOS is based on two considerations. First, the majority of the drug candidates are low-mass molecules. In MALDI, the matrix is essential to desorption/ionization, but the use of matrix also generates strong matrix-related background noise in the low-mass region, which obscures or even suppresses the analytical signals of other low-mass molecules. In contrast, a matrix is not required for DIOS and laser desorption/ionization is performed on porous silicon, therefore eliminating the matrix-related background problem. DIOS is very effective for analysis of low-mass molecules. Second, DIOS involves the use of porous silicon as a probe on which proteins can easily be immobilized. Furthermore, the porous silicon probe can be generated routinely through electrochemical anodization^[15, 16] or chemical etching^[17–19] of flat crystalline silicon. The porous silicon surface can be regenerated easily.

A silicon wafer was galvanostatically etched and oxidized. The preparation of a good porous silicon probe is essential for the success of this assay, as only well-etched silicon wafers produce good ion signals by laser desorption/ionization without the use of matrix. We have a porous silicon probe for the routine generation of good mass spectra of a variety of drugs, including atropine, propranolol, atenolol, alprenolol, metoprolol, warfarin, sulpride, naproxen, and ketoprofen. Figure 1 shows the mass spectrum^[20] of naproxen obtained when using a) MALDI with 2,5-dihydroxybenzoic acid (DHB) as matrix and b) the DIOS technique. Clearly, a number of strong matrix-related peaks were present in the mass spectrum when a DHB matrix was used (Figure 1 a). In contrast, the only major peak in the DIOS spectrum (Figure 1 b) corresponds to naproxen and, importantly, no fragmentation of naproxen was observed in DIOS. We have also been able to produce good mass spectra of a variety of peptides of less than 500 Da by means of DIOS. Furthermore, we have successfully used this method to detect the products of the derivatization of cyclodextrin.

Because many drug molecules are good binding partners of bovine serum albumin (BSA), we tested this new direct binding assay with BSA. BSA was immobilized on the porous silicon probe with 2,4,6-trichloro-1,3,5-triazine as the activated agent. The experimental procedure for the immobilization

[*] Prof. H. Zou, Q. Zhang, Z. Guo, Q. Zhang, X. Chen
 National Chromatographic R&A Center
 Dalian Institute of Chemical Physics, Chinese Academy of Sciences
 Dalian 116011 (China)
 Fax: (+86) 411-369-3407
 E-mail: zouhfa@mail.dlptt.ln.cn

Prof. B. Guo
 Department of Chemistry, Cleveland State University
 Cleveland, OH 44115 (USA)

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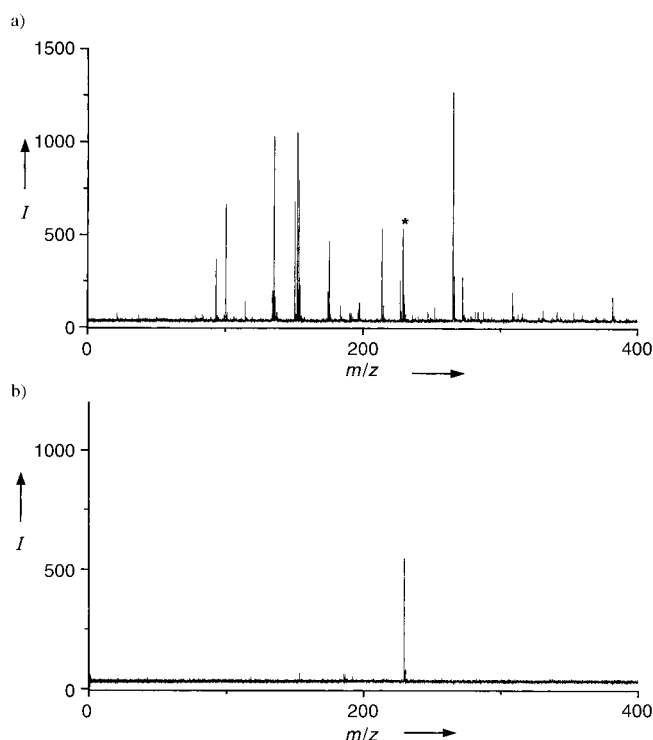


Figure 1. Mass spectra of naproxen ($M = 230.26$): a) MALDI with DHB as matrix (* = naproxen) and b) DIOS (sample deposited on porous silicon).

of BSA on porous silicon to obtain the biologically active BSA surface has been reported previously.^[21] The experimental protocol for preparing the probe is outlined in Figure 2: generation of porous silicon, covalent linking of BSA, and washing the treated probe with suitable solvents such as ethanol (10 %).

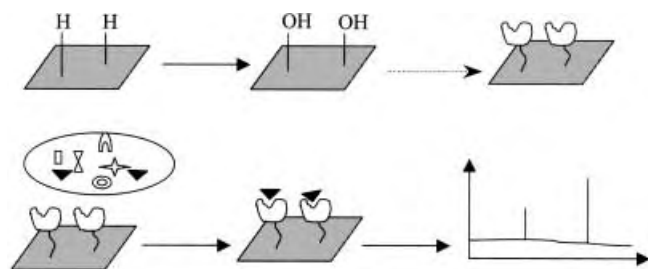


Figure 2. Experimental protocol for the mass spectrometry based direct-binding assay on protein-immobilized porous silicon wafers.

A solution (2 μL) of ketoprofen (6.0 mg mL^{-1}) and sulpride (5.0 mg mL^{-1}) was incubated with the immobilized BSA probe for about 2 min. Thereafter, the probe was washed with ethanol (20 %, 20 μL) to remove the molecules that were not captured by the immobilized BSA. Finally, the probe was inserted into the mass spectrometer for analysis. Figure 3a shows a typical mass spectrum obtained by using this procedure. The only signal observed corresponds to ketoprofen and no signal for sulpride was present (Figure 3a), which clearly shows that ketoprofen was captured by the immobilized BSA, whereas sulpride was not. This result, in turn,

reveals that ketoprofen is a good binding partner of BSA, whereas sulpride is not.

For comparison, the probe without the immobilized BSA was also investigated. The same sample used to measure the mass spectrum in Figure 3a was deposited on the probe, but the probe was not washed with ethanol. The signals of both ketoprofen and sulpride were observed (Figure 3b). However, when the probe without the immobilized BSA was washed with ethanol (20 %, 20 μL), the signals from both ketoprofen and sulpride were no longer observable in the mass spectrum (Figure 3c). This comparison experiment further confirms the fact that the immobilized probe captures only the binding partner of the target protein.

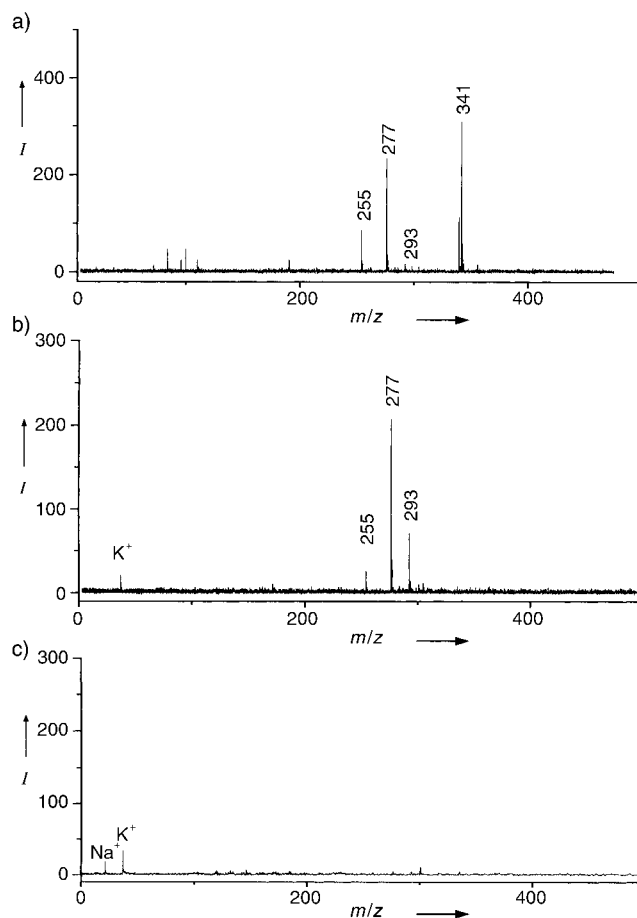


Figure 3. Mass spectra of ketoprofen and sulpride on a BSA-immobilized affinity probe: a) ketoprofen (the peaks at $m/z = 255, 277, 293$ indicate $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$, respectively) and sulpride ($M = 341$) deposited on freshly etched porous silicon, b) ketoprofen and sulpride deposited on the probe (not immobilized with BSA), and c) ketoprofen and sulpride deposited on freshly etched porous silicon, and washed with ethanol (20 %, 20 μL).

This new assay can also be used to probe the relative binding affinity of different ligands to a target protein. For example, we applied this assay to analyses of mixtures of propanolol (8.9 mg mL^{-1}) and atenolol (4.6 mg mL^{-1}). When the sample was incubated with the BSA-immobilized probe, followed by washing with ethanol (10 %, 10 μL), a strong signal for each of the molecules was observed in the mass spectrum (Figure 4a). This suggests that both propanol and

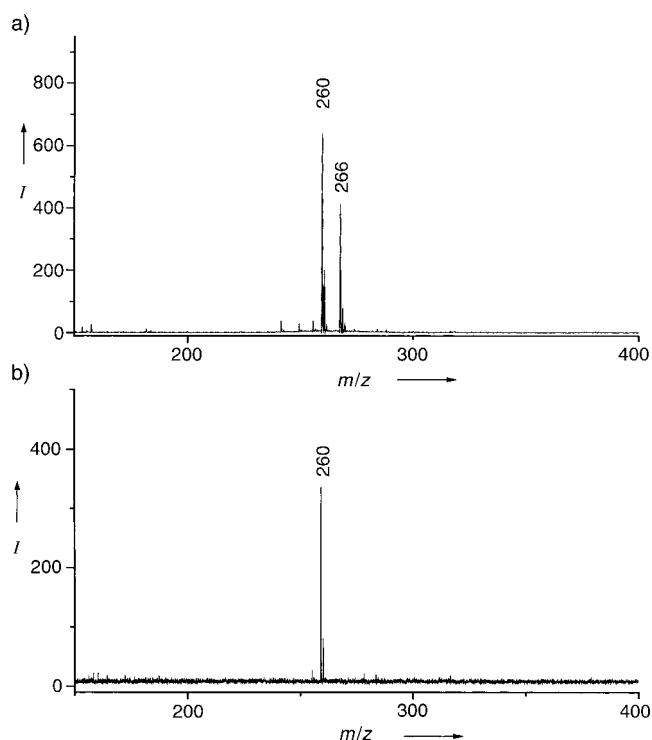


Figure 4. Mass spectra of propranolol and atenolol deposited on the BSA-immobilized affinity probe and washed with a) ethanol (10 %, 10 μ L), and b) ethanol (10 %, 30 μ L).

atenolol were captured by BSA under these conditions. However, when the probe was washed with 30 μ L rather than 10 μ L of ethanol (10 %), the peak of atenolol ($M=267$) disappeared from the spectra, whereas the peak of propranolol was still present (Figure 4b). This may reflect the fact that propranolol has a stronger affinity for BSA than does atenolol. To validate this argument, we studied the binding affinity of these two drugs for BSA by using a chromatographic column packed with BSA-immobilized silica. We found that propranolol was retained more strongly than atenolol in the column, thus confirming that propranolol has a stronger affinity for BSA than does atenolol.

In summary, we have presented a novel direct binding assay for fishing the binding partner of a target protein. In this assay, the porous silicon probe not only captures the binding partner of the immobilized protein, but also serves as the substrate for direct laser desorption/ionization, thereby eliminating the matrix-related background problems. As a result, the captured molecules can be directly identified on probe by means of mass spectrometry. This assay does not require fluorescence tags, radioactive markers, or even prior purification. The major application of this new assay is in the drug discovery process. The strength of this assay may be particularly useful in high-throughput screening of lead-drug candidates. For example, this assay can be used to screen large compound libraries. It can also be used to fish the active ingredients present in natural products such as Chinese medicines.

The directed binding assay presented herein may not be limited to the study of protein targets and may be modified to study the binding partners of other biomolecules, including

DNA, RNA, antibodies, lipids, peptides, and whole cells. This assay can be upgraded to a chip-based assay in which a number of proteins or other biomolecules are immobilized on the same probe to search for lead drug candidates for multiple targets.

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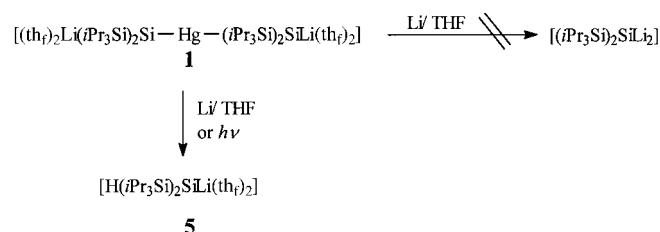
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and the two $\text{Li}(\text{thf})_2$ groups), as well as the absence of strong electronic effects of the Si–Li bonds on the Si–Hg bonds. The Si–Li bond length (2.558(1) Å) is similar to the Si–Li bond length in $[(i\text{Pr}_3\text{Si})_2\text{Si}(\text{Li}(\text{thf})_2)]$ (2.550 Å),^[3] but significantly shorter than the usual Si–Li bond length in solvated silyllithium reagents (2.64–2.77 Å).^[2, 8] This difference may be because each lithium atom is solvated by only two THF molecules, while in other $[\text{R}_3\text{SiLi}]$ compounds three molecules of THF are coordinated to Li atom.^[8c]

The NMR spectroscopic data of **1** provides information about its electronic structure. The ^{199}Hg chemical shift in **1** is $\delta = 1271$, the most deshielded value known. The previously most deshielded value of $\delta = 1142$ was reported by us for $[(\text{Me}_3\text{SiMe}_2\text{Si})_3\text{Si}]_2\text{Hg}_2$.^[9] The ^{29}Si chemical shift of Si1 atom bonded to both Hg and Li, is -120.7 ppm, strongly shielded compared to $[(\text{Me}_3\text{Si})_3\text{Si}]_2\text{Hg}$ (-54.5 ppm),^[10] but it is less shielded than in $(\text{Me}_3\text{Si})_3\text{SiLi}(\text{thf})_3$ ($\delta = -189.4$)^[11] and in $[(i\text{Pr}_3\text{Si})_2\text{Si}(\text{Li}(\text{thf})_2)]$ ($\delta = -292.0$).^[3]

Treatment of **1** with excess of Li in THF did not lead to the expected complex $[(i\text{Pr}_3\text{Si})_2\text{SiLi}_2]$. Instead a new silyllithium reagent, $[\text{H}(i\text{Pr}_3\text{Si})_2\text{SiLi}(\text{thf})_2]$ (**5**), was obtained as the major product (Scheme 2). The mechanism of this intriguing reaction is under current study.



Scheme 2. Lithiation or irradiation of **1**.

Irradiation of **1** in hexane also yields **5** as the major product (Scheme 2). The EPR spectrum observed during the irradiation of **1** (Figure 2) can be interpreted as a superposition of the signals of three radicals: the first silyl radical with an α -Si–Li bond $[(i\text{Pr}_3\text{Si})_2\text{LiSi}]^\bullet$ (**6**), silyl radical $(i\text{Pr}_3\text{Si})_2\text{HSi}^\bullet$ (**7**), and the Hg-substituted radicals $[\text{RLi}(i\text{Pr}_3\text{Si})_2\text{SiHg}(i\text{Pr}_3\text{Si})_2\text{Si}]^\bullet$ (**8**, $\text{R} = \text{H}$ or Li).^[12] The structure of **6** is confirmed by the presence of a quartet centered at $g = 2.0073$ resulting from interaction of the unpaired electron with a ^7Li nuclei ($I = 3/2$) and two quartets of satellites resulting from interaction of the unpaired electron with the α - and β - ^{29}Si nuclei and a further splitting by interaction with the ^7Li nuclei $a(^7\text{Li}) = 1.25$ G (Figure 2c). The hyperfine coupling constant (hfc) value $a(^{29}\text{Si}(\alpha)) = 32.0$ G is intermediate between the α constants measured for branched $(\text{R}_3\text{Si})_3\text{Si}^\bullet$ radicals (55.6–63.8 G)^[4, 13] and for cyclic polysilyl anion radicals, $[\text{c}-(\text{R}_2\text{Si})_{4-6}]^\bullet$ (5.0–7.0 G).^[14, 15] Quantum-mechanical calculations^[16] are consistent with the observed hfc in **6**. Thus, for the model radical $[(\text{Me}_3\text{Si})_2\text{LiSi}]^\bullet$, which has a planar geometry around the central Si atom, the calculations predict $a(^{29}\text{Si}(\alpha)) = 30.2$ G and $a(^7\text{Li}) = 1.0$ G, in good agreement with the experimental values of **6**. It is of note that the calculated $a(^{29}\text{Si}(\alpha)) = 8.7$ G for $(\text{Me}_3\text{Si})_2\text{Si}^\bullet$ is much lower than for

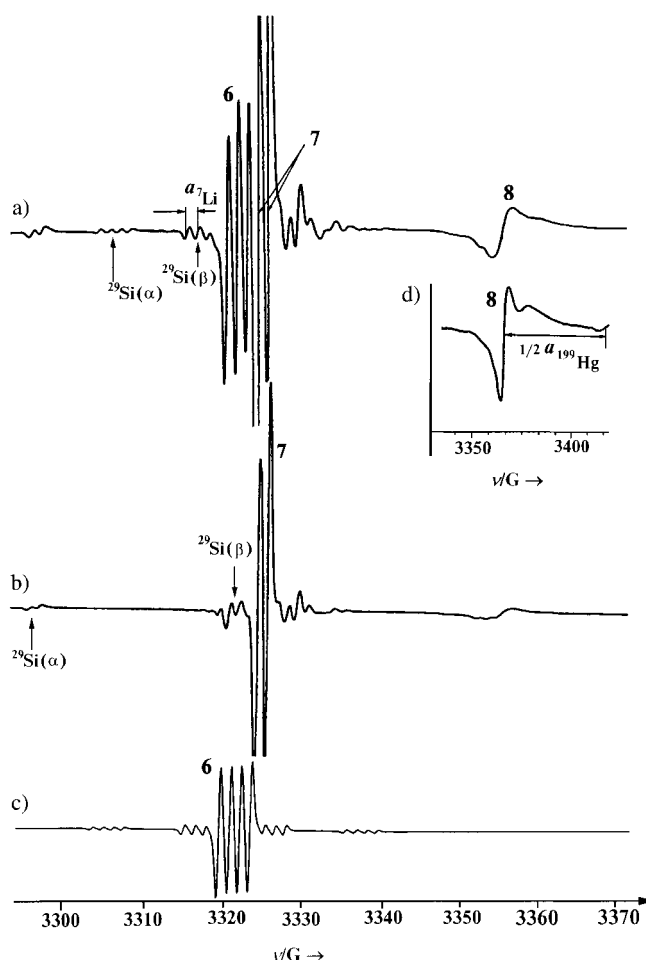


Figure 2. Experimental EPR spectra in hexane at 300 K and simulated EPR spectra: a) The spectrum observed during UV irradiation of **1**. b) The spectrum of silyl radical $\text{H}(i\text{Pr}_3\text{Si})_2\text{Si}^\bullet$ (**7**) after the UV irradiation was stopped. c) Computer simulation of the EPR spectrum of the silyl radical $[\text{Li}(i\text{Pr}_3\text{Si})_2\text{Si}]^\bullet$ (**6**) using the $a(^7\text{Li}) = 1.25$ G, $a(^{29}\text{Si}(\alpha)) = 32.0$ G, and $a(^{29}\text{Si}(\beta)) = 10.0$ G as parameters (see discussion). d) (Inset) Upfield components of possible radicals $[\text{R}(i\text{Pr}_3\text{Si})_2\text{SiHg}(i\text{Pr}_3\text{Si})_2\text{Si}]^\bullet$ (**8**, $\text{R} = \text{Li}$ or H).

$(\text{Me}_3\text{Si})_2\text{LiSi}^\bullet$. The observed hyperfine interaction of the unpaired electron with ^7Li nucleus indicates that the Si–Li bond in **6** does not dissociate in solution. This proposal is also supported by the high $a(^{29}\text{Si}(\alpha))$ value of 32.0 G in **6**, because if **6** did dissociate to $(\text{Me}_3\text{Si})_2\text{Si}^\bullet$ and Li^+ ions a much lower $a(^{29}\text{Si}(\alpha))$ of around 9 G would be expected.

Experimental Section

Standard Schlenk techniques were used for all syntheses and all sample manipulations.

1: $[\text{tBu}_2\text{Hg}]$ (13.5 g 43.0 mmol) were added under argon to $(i\text{Pr}_3\text{Si})_2\text{SiH}_2$ ^[19] (10.0 g, 29.0 mmol) in three equal portions while heating the mixture to 120 °C. A new portion of $[\text{tBu}_2\text{Hg}]$ was added after complete evolution *isobutane* from the reaction mixture (approximately every 4 h). After evaporation of the volatile compounds, THF (50 mL) and Li powder (7.0 g, 1.0 mol) were added and the mixture was stirred at RT for 1 h. The mixture was decanted from the lithium powder and the solvent was evaporated. Crystallization from hexane gave (11.2 g, 9.4 mmol) of green crystals of **1** in 65 % yield.

^1H NMR (200 MHz, C_6D_6): $\delta = 1.51$ (br m, 100H), 3.54 (t, 16H; CH_2O); ^{13}C NMR (200 MHz, C_6D_6): $\delta = 17.6$ (Me_2CH), 22.0 (Me_2CH), 25.3 ($\text{CH}_2-\text{CH}_2\text{O}$), 68.5 ($\text{CH}_2-\text{CH}_2\text{O}$); ^{29}Si NMR (400 MHz, C_6D_6): $\delta = -120.9$



((iPr₃Si)₂Si), 30.23 ((iPr₃Si)₂Si); ¹⁹⁹Hg NMR (400 MHz, C₆D₆): δ = 1271.6. Methylation of **1** with MeCl gave **3** (90%). **3**: ¹H NMR (C₆D₆): δ = 0.69 (s, 6H; Si-Me), 1.25 (d, ³J(H,H) = 5.8 Hz, 72H; Me₂CH), 1.54 (m, ³J(H,H) = 5.8 Hz, 12H; Me₂CH); ¹³C NMR (C₆D₆): δ = -1.7 (Si-Me), 15.3 (Me₂CH), 20.8 (Me₂CH), 21.0 (Me₂CH); ²⁹Si NMR (C₆D₆): δ = -25.1 ((iPr₃Si)₂Si), 18.1 ((iPr₃Si)₂Si); ¹⁹⁹Hg NMR (C₆D₆): δ = 501.0; MS(Cl) *m/z* 916 (*M*⁺); m.p. 186 °C (decomp., evacuated capillary). Hydrolysis of **1** gave **4** (95%). **4**: ¹H NMR (C₆D₆): δ = 1.24 (d, ³J(H,H) = 2.3 Hz, 72H; Me₂CH), 1.41 (m, ³J(H,H) = 5.8 Hz, 12H; Me₂CH) 3.73 (s, 2H; SiH); ¹³C NMR (C₆D₆): δ = 15.2 (Me₂CH), 20.4 (Me₂CH), 20.5 (Me₂CH); ²⁹Si NMR (C₆D₆): δ = -81.5 ((iPr₃Si)₂Si), 24.0 ((iPr₃Si)₂Si); ¹⁹⁹Hg NMR (C₆D₆): δ = 691.0; MS(Cl) *m/z* 888 (*M*⁺); m.p. 204 °C (decomp., evacuated capillary). Lithiation of **1** with Li powder in THF for 1 h at RT gave **5** (75%) after crystallization from pentane. **5**: ¹H NMR (C₆D₆): δ = 1.41 (br m, 50H; (CH₃)₂CH₂-CH₂-O), 3.50 (t, m, 9H; CH₂-O, SiH); ¹³C NMR (C₆D₆): δ = 15.8 (Me₂CH), 21.3 (Me₂CH), 25.4 (CH₂-CH₂-O), 68.4 (CH₂-CH₂-O); ²⁹Si NMR (C₆D₆): δ = -205.4 ((iPr₃Si)₂Si), 20.8 ((iPr₃Si)₂Si).

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Autonomous Movement and Self-Assembly**

Rustem F. Ismagilov, Alexander Schwartz,
Ned Bowden, and George M. Whitesides*

Many complex systems—from swarming bacteria and schooling fish to transportation networks and capital markets—show a number of characteristics in common, among which are autonomous movement of the components of these systems, and interactions (which can be both attractive and repulsive) among these components.^[1] We have begun a program to explore complexity by designing and fabricating/synthesizing components that both *move* and *interact* with one another, and then characterizing the patterns that emerge from groups of these components. As part of this program, we wish to develop entities capable of *autonomous* movement, and to explore the collective behaviors of these entities in motion. This paper describes the behavior of small (<1 cm) hemicylindrical plates that have a small area of platinum on one surface and that float at the surface of an aqueous solution of hydrogen peroxide. These plates moved under the impulse of bubbles generated by the platinum-catalyzed decomposition of hydrogen peroxide ($2\text{H}_2\text{O}_{2(l)} \rightarrow \text{O}_{2(g)} + 2\text{H}_2\text{O}_{(l)}$).^[2] The edges of these plates were also patterned to have hydrophobic and hydrophilic regions; capillary interactions between menisci at the hydrophobic edges attract the plates to one another. We have shown previously that capillary interactions can cause the assembly of periodic 2D and 3D structures in systems of particles with sizes ranging from 10 μm to several millimeters.^[3]

Autonomous movement occurs in many animate systems and a surprising number of inanimate ones. Animate movement is normally due to the action of rotary and linear molecular motors—driven by the dissipation of ion gradients across membranes or by the hydrolysis of ATP.^[4] Inanimate motion takes a wide variety of forms, with the simplest systems often taking advantage of gradients in concentration or temperature. Self-propulsion of camphor crystals placed on an air/water interface occurs by preferential dissolution of camphor from one of the sides of the crystal; this dissolution creates a gradient in surface tension of the air/water interface and induces motion.^[5] Gels swollen with an organic solvent (such as ethanol or tetrahydrofuran) can move when slow injection of the solvent at one face of the gel locally reduces the surface tension.^[6] Marangoni effects can generate motion in fluids or droplets under a variety of circumstances:^[7] for example, a fluid film heated by a solid surface on one side and cooled by air on the other side spontaneously develops convection cells in which fluid motion transfers heat from the

warmer to the cooler surface.^[8] There are many other chemical systems that generate motion. A mercury droplet placed in proximity to a dissolving potassium dichromate crystal in water shows motion in the developing concentration gradient of the oxidant.^[9] Pieces of sodium move on the surface of water while dissolving and reacting.^[10] Tin clusters show complex motion on copper surfaces while alloying with the substrate.^[11] These systems are all conceptually related and, although their components move, they do not offer a clear opportunity for the design of systems with motion and interactions that can be tailored. Most also suffer from the disadvantage that they consume or dissipate a material stored “on board” and are thus limited in the duration over which they can move and in the constancy of that motion.

We have designed a system in which the components move autonomously by ejecting small bubbles of gas formed by catalytic decomposition of a liquid. The fuel (or “food”) required for motion is thus present in the environment and can, in principle, sustain motion indefinitely. Metallic platinum is an excellent catalyst for the decomposition of hydrogen peroxide into water and dioxygen. Under the conditions used in the experiments described herein, the action of this catalytic system is approximately constant over two hours, or five times the interval of time required to complete the experiments shown in the Figures. Plates floating in a container with a large amount (1 L) of the aqueous solution of hydrogen peroxide continued moving for several days, albeit with a slow decrease in velocity due to the depletion of H_2O_2 in solution; motion could be restored to its original level by replenishing the H_2O_2 .

Self-propulsion. Self-propelling plates were fabricated from polydimethylsiloxane (PDMS) using rapid prototyping;^[12] Figure 1A shows the design. The plates were placed at the

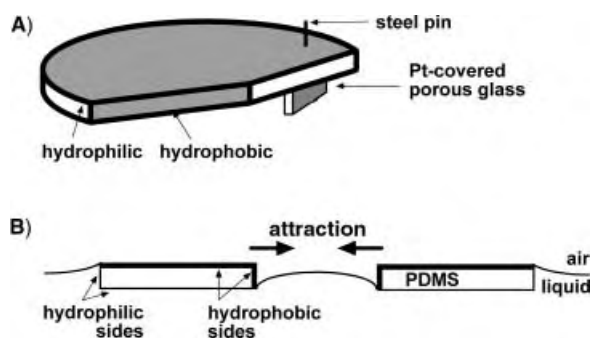


Figure 1. A) Schematic of a self-propelling object. A thin plate (circa 1–2 mm thick and 9 mm in diameter) was fabricated from PDMS in a desired shape, and specified faces were rendered hydrophilic by oxidation in a plasma formed in air. A $2 \times 2 \text{ mm}^2$ piece of porous glass filter (covered with platinum by an electron beam evaporation) was mounted on the PDMS piece with a stainless steel pin. B) A diagram illustrating self-assembly by capillary interactions.

[*] Prof. G. M. Whitesides, Dr. R. F. Ismagilov,
Dr. A. Schwartz, N. Bowden
Department of Chemistry and Chemical Biology
Harvard University
12 Oxford St., Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-9857
E-mail: gwhitesides@gmwhgroup.harvard.edu

[**] This work was supported by DoE under grant 00ER45852. The salary of R.F.I. was provided by the DARPA and NSF under grant NSF ECS-9729405; the salary of A.S. was provided by the NSF under grant NSF CHE-9901358.

liquid/air interface of a 1–3% aqueous solution of H_2O_2 at room temperature. The evolution of gaseous O_2 began immediately and caused motion of the plates. These plates moved on the surface of H_2O_2 with velocities of up to $1\text{--}2 \text{ cm s}^{-1}$ for several hours. This motion was reproducible for all plates in a group of 20 plates. The energy required for



movement comes from the recoil of the liquid as the bubbles burst.

Self-assembly. The hydrophobic sides of PDMS plates floating at a H_2O_2 /air interface create negative menisci.^[3a] When two such objects approach each other more closely than the capillary length (on the order of several millimeters), the menisci overlap and interact, and the objects are attracted to each other (Figure 1B). The attraction is caused by the decrease in the total area of the H_2O_2 /air interface, and the attractive force is proportional to the surface tension of that interface. Because the chemical reaction that is taking place on the plates does not significantly affect the surface tension of the liquid, surface tension driven self-assembly can take place in our system.

Chiral self-assembly. The hemicylindrical plates used in self-assembly (Figure 1A) are chiral because the catalyst attached to a disk breaks both the left–right and top–bottom symmetries. A single plate rotates in the direction determined by its chirality (Figure 2). The direction of this rotation was reproducible for all plates (in a set of 20), but the frequency, the radius of curvature, and the position of the center of rotation differed slightly from plate to plate. This irregularity of motion of single plates is also visible prior to their self-assembly in pairs (Figure 3). We have designed these plates so they could assemble in pairs of two configurations: a) Plates of the opposite chirality can assemble into heterochiral dimers (Figure 3A); b) plates of the same chirality can assemble into homochiral dimers (Figure 3B). The heterochiral dimer moves unidirectionally, in contrast to the rotational motion of individual plates. The average velocity of this dimer is 2–3 times higher than that of the individual plate (Figure 3A). The homochiral dimer rotates in the same direction as its individual plates, although its rotation is more regular than that of the isolated plates (Figure 3B).

Figure 2. Overlaid photographic images that show catalytic self-propulsion of a single plate of the type shown schematically in Figure 1. On this and the following Figures, white dots were added onto the photographs to indicate the catalyst-bearing tips of the plates.

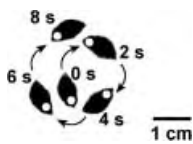


Figure 3B also shows that motion ensures that plates assemble into the most stable configuration. At $t = 38$ s two plates assemble into a metastable configuration that persists until $t = 52$ s (not shown) and then rearranges into the stable configuration (with maximum hydrophobic–hydrophobic contact) at $t = 54$ s. We base our assignment of the relative stability of the two configurations on the fact that we have never observed the reverse rearrangement to occur.

We also wished to establish whether interactions of larger number of plates could lead to a different type of collective behavior. When ten plates (five of each chirality) were allowed to float on the surface of hydrogen peroxide, four pairs assembled in approximately 20 min (Figure 4) with no pronounced selectivity in assembly for homochiral versus heterochiral dimers (four experiments). The last pair did not assemble in the next 20 minutes, and we attribute this fact to the decrease in the rate of assembly as the surface density of single plates decreased.^[13] These results indicate that inter-

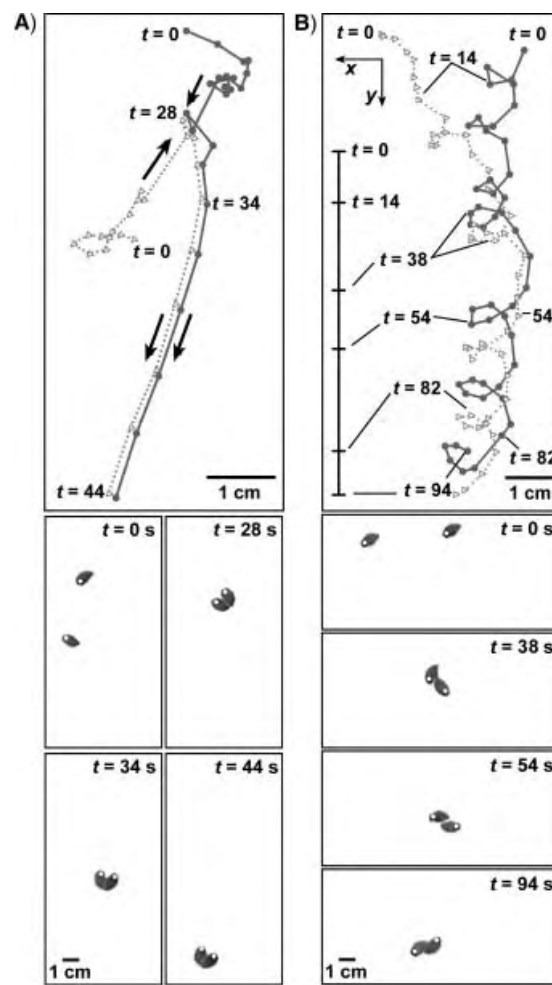


Figure 3. Graphs and images that illustrate motion and self-assembly of self-propelling plates (shown in Figure 1A) in 3% H_2O_2 . On graphs, the symbols indicate the position of the piece at two-second intervals. A) Two plates of opposite chirality assemble into a dimer that moves translationally. On the graph, the symbols correspond to the position of the tip of the plate that does not bear the catalyst. B) Two plates of same chirality assemble into a dimer that moves rotationally. On the graph, the symbols correspond to the position of the catalyst-bearing tip of the plate. To deconvolute the rotational motion, we have transformed the vertical y -axis [cm] of the plot to a new y' axis that shows both the position on the y coordinate and time t [s] using the relation $y' = y + 0.1t$. This stretching of the y -coordinate with time allows us to show the last three cycles of the rotational motion of the aggregate; in fact, these three cycles of rotation occur around a center that is approximately fixed. Bars crossing the vertical line correspond to the position of a stationary point at $t = 0, 14, 38, 54, 82$, and 94 s.

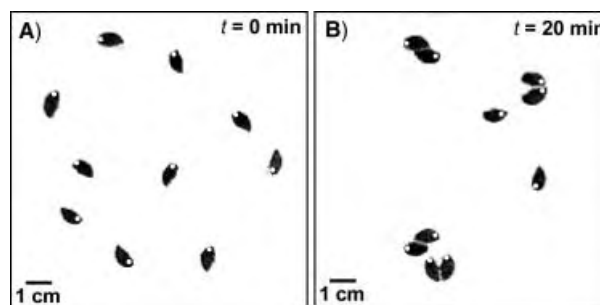


Figure 4. Photographs showing self-assembly of 10 plates (5 of each chirality). Initially (A), isolated plates were randomly distributed. In approximately 20 minutes (B), 4 pairs assembled into dimers.



actions of five pairs of plates do not lead to an additional level of complexity; larger numbers of plates, or plates designed to have multiple interactions, may be required before the system shows unexpected ("emergent") behavior.^[14]

This paper is the first step towards our goal of creating artificial complex systems composed of large numbers of components that move autonomously, and that self-assemble. To achieve the goal, we must design a system in which we can control both motion and self-assembly, and must make components small enough so that interactions of large numbers of them can be studied. This paper describes the first artificial system of autonomously moving and self-assembling components in which the interactions among the components can be controlled through their design. This system has three advantages: a) The plates can be designed to move at a controlled velocity in different environments with a range of concentrations of the fuel, because the rate of decomposition can be controlled by controlling the amount and the activity of the catalyst; b) The plates can be made to assemble into aggregates of different stability because the strength of capillary interactions among the plates can be controlled through the thickness of the plates, their density, and the hydrophobicity of their surfaces; c) The energy required for motion is derived from the environment rather than from limited supply of fuel stored inside the plates, and the plates can therefore be made small yet still move over long periods of time. The disadvantage of the system is that all the processes take place at a fluid/air interface and are confined to two dimensions. If the system were transferred into the bulk of the solution, bubbles formed by the decomposition of the solution would affect the buoyancy of the plates and would make their motion more complicated and less predictable.

Self-assembly of autonomously moving components may find applications in the bottom-up fabrication of small functional systems. In addition, it suggests applications as a new type of self-assembly—one in which the products of self-assembly sort themselves. For example, our method of self-assembly forms heterochiral dimers with a statistically expected 50% yield, but there is a difference in the behavior of the dimers: Both the single plates and homochiral dimers rotate approximately in place, while the heterochiral dimers move in straight lines. Even though the self-assembly proceeds with a 50% yield, the system is one in which the heterochiral and homochiral dimers can separate themselves because the heterochiral dimer can swim out of the mixture of plates and dimers.

In examining emergence in a system, an important question is "How many interacting components are required in order for the system to show behavior that is not predicted from the properties of the components?" In this system, a new property (motion in a straight line), not present in the separate components, appears upon assembly of just two plates into a heterochiral dimer. We believe that assemblies of a moderate number of components—tens or hundreds—may show substantially more complex behaviors, but still be amenable to controlled experimentation. Such systems could find technological applications, and could help to understand behavior of other complex systems characterized by large number of

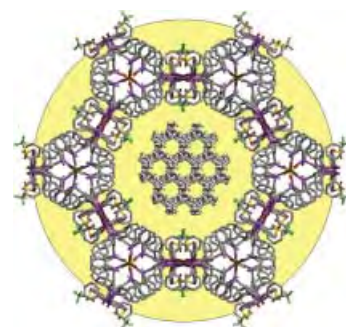
autonomously moving, interacting components (for example schooling fish and swarming bacteria).

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- [13] This lack of assembly is not due to the loss of hydrophobicity of PDMS in H_2O_2 . Floating on the surface of 3% H_2O_2 for 2 h did not affect the propensity of the plates to assemble—20 plates out of the batch of 20 formed stable dimers with each other.
- [14] We use the word "emergence", although it is not clear yet whether emergence is a fundamentally new concept, or a word with which to describe systems that are not yet understood but can be understood in principle.

COVER PICTURE

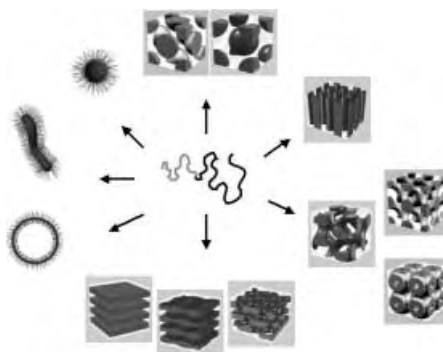
The cover picture shows an unusually wide (16 Å) channel in a stable nanoporous coordination framework, which is also novel in being based on bridging phosphane ligands. A space-filling representation of a segment of the structure is shown at the center of the picture. The as-synthesized material contains disordered ethanol guests, which can be exchanged for other solvents, and subsequently the material was obtained virtually guest-free, without structural collapse. The unconventional use of a phosphane enabled information to be gained on this framework's solution-based precursors (by ^{31}P NMR spectroscopy) which appear to be discrete coordination cages. Further details are reported by S. L. James and co-workers on p. 764 ff.



REVIEWS

Contents

A large number of superstructures with characteristic dimensions in the range of a few nanometers up to several micrometers are formed by the self-organization of block copolymers (see picture). Possible applications in the fields of materials science and molecular biology are currently being intensively investigated. Their range of application extends from the production of inorganic nanoparticles and mesoporous materials up to take-up/release systems in chemo- and gene therapy.



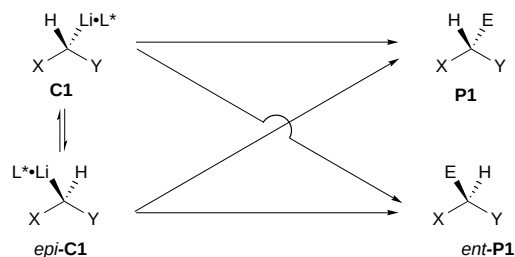
S. Förster,* T. Plantenberg 688–714

From Self-Organizing Polymers to
Nanohybrid and Biomaterials

Keywords: amphiphiles • hybrid
materials • nanostructures • polymers •
self-organization

Angew. Chem. **2002**, 114, 712–739

Chiral organolithium compounds are versatile intermediates with numerous applications in asymmetric synthesis. They range widely in their configurational stability and in the stereochemistry of their electrophilic substitution. Effective transfer of stereochemical information from the lithiated intermediate (**C1** and *epi-C1*) to the final product (**P1** and *ent-P1*) is dependent on the interplay between these two factors.



Angew. Chem. **2002**, *114*, 740–763

A. Basu,* S. Thayumanavan* . 716–738

Configurational Stability and Transfer of Stereochemical Information in the Reactions of Enantioenriched Organolithium Reagents

Keywords: asymmetric synthesis • configuration determination • electrophilic substitution • enantioselectivity • lithium

ESSAY

Has translation a central role in the present and future of science? After showing the importance of translating in the past, in the way the names of the chemical elements were transferred (from Dutch sources) to Japanese, the author tries to answer the above question. His conclusion is that today's dominance of English imposes an increased need for translation, as 1) the major portion of the secondary literature in any country is published in that nation's language, 2) in cases where English is the destination language for publication, scientists in many non-English speaking nations report their primary research in their mother tongue and then have to translate their results into English for submission, and 3) research has to be communicated to non-scientists, including the public, the mass media, educators, political leaders, and other decision makers.

Angew. Chem. **2002**, *114*, 765–768

S. L. Montgomery* 739–742

Chemical Transformations: Translation and the Periodic Table in Japan

Keywords: history of science • periodic table • translation

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>

Enantioselective Synthesis of the Kedarcidin Chromophore Aglycon in a Differentially Protected Form

A. G. Myers,* P. C. Hogan, A. R. Hurd ◆

Surface Structure and Crystal Growth in Zeolite Beta C

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

Semiconductor Nanohelices Templated by Supramolecular Ribbons

E. D. Sone, E. R. Zubarev, S. I. Stupp*

Phase-Sensitive Supramolecular Chirogenesis in Bisporphyrin Systems

V. V. Borovkov,* T. Harada, Y. Inoue, R. Kuroda*

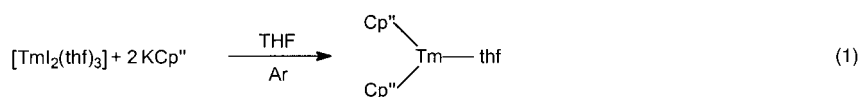
The Stable Pentamethylcyclopentadienyl Cation

J. B. Lambert,* L. Lin, V. Rassolov

Polymeric Surfactants for the New Millennium: A pH-Responsive, Zwitterionic, Schizophrenic Diblock Copolymer

S. Liu, S. P. Armes*

That previously unattainable organolanthanide(II) complexes may be accessible through judicious manipulation of reaction conditions and supporting ligands is suggested by the recent isolation of the organothulium(II) compound $[\text{Cp}''_2\text{Tm}(\text{thf})]$ [Eq. (1); $\text{Cp}'' = \eta^5\text{-C}_5\text{H}_3\text{-1,3-(SiMe}_3)_2$]. In light of the diverse reactions mediated by Sm^{II} compounds it seems likely that these new compounds will provide a useful addition to the armory of reagents available to the synthetic chemist.



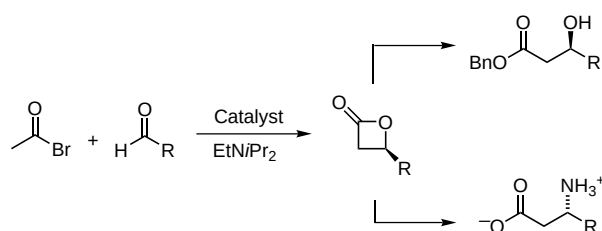
Angew. Chem. **2002**, *114*, 769–770

K. Izod* 743–744

A New Era in Divalent Organolanthanide Chemistry?

Keywords: cyclopentadienyl ligands • dysprosium • lanthanides • metallocenes • thulium

Owing to their highly strained ring system and interesting functional group, β -lactones possess significant synthetic potential. Recently, novel methods have been developed to synthesize these valuable building blocks very efficiently by catalytic, enantioselective reactions, such as [2+2] cycloadditions, starting from simple precursors. These processes also offer an attractive alternative for the synthesis of optically active β -hydroxy and β -amino acids (see scheme).



Angew. Chem. **2002**, *114*, 771–772

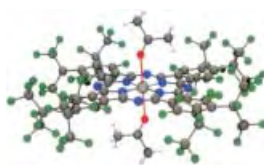
C. Schneider* 744–746

Catalytic, Enantioselective Syntheses of β -Lactones—Versatile Synthetic Building Blocks in Organic Chemistry

Keywords: asymmetric catalysis • cycloaddition • lactones • small ring systems

COMMUNICATIONS

A higher anticancer activity is observed in photodynamic tests with the first sterically bulky (non-planar) perhalogenated zinc phthalocyanine (Pc), $[\text{F}_{64}\text{PcZn}(\text{acetone})_2]$ (see structure: F green, N blue, O red, C gray) in comparison with planar zinc perfluorophthalocyanine. The perfluoroisopropyl substituents enhance the solubility, stabilize axial ligands (such as the coordinated acetone molecules in the structure shown), narrow the HOMO–LUMO gap, shift redox potentials, and increase the lifetime of the excited triplet state of the new complex.



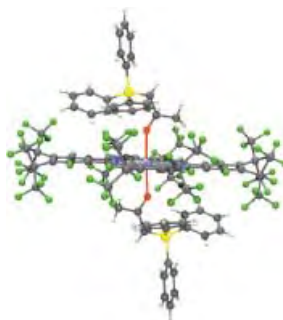
Angew. Chem. **2002**, *114*, 773–776

B. A. Bench, A. Beveridge, W. M. Sharman, G. J. Diebold,* J. E. van Lier,* S. M. Gorun* .. 747–750

Introduction of Bulky Perfluoroalkyl Groups at the Periphery of Zinc Perfluorophthalocyanine: Chemical, Structural, Electronic, and Preliminary Photophysical and Biological Effects

Keywords: fluorinated ligands • photodynamic therapy • phthalocyanines • zinc

An enzyme-inspired phthalocyanine (Pc) complex $[\text{F}_{64}\text{PcCo}(\text{acetone})_2]$ is the first representative of a novel class of robust homogeneous catalysts. This complex couples aryl and alkyl phosphanes with acetone to catalytically produce ylides (the structure shows the ylide coordinated to the F_{64}PcCo unit: F green, N blue, O red, C gray, P yellow) and water under ambient conditions using only air, a route that avoids the classical use of halogenated intermediates.



Angew. Chem. **2002**, *114*, 776–780

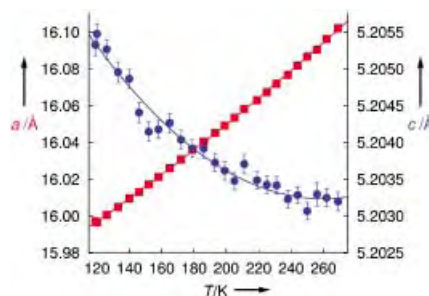
B. A. Bench, W. W. Brennessel, H.-J. Lee, S. M. Gorun* 750–754

Synthesis and Structure of a Biconcave Cobalt Perfluorophthalocyanine and Its Catalysis of Novel Oxidative Carbon–Phosphorus Bonds Formation by Using Air

Keywords: cobalt • fluorinated ligands • homogeneous catalysis • phthalocyanines • ylides

A helix that expands on cooling:

The crystal structure of TrpGly·H₂O consists of helical peptide nanotubes extending throughout the crystal. The thermal expansion is negative in the helical direction (see graph; *a* axis: red, *c* axis: blue). This effect is believed to be linked to the increasing order of water molecules enclosed in the helices.



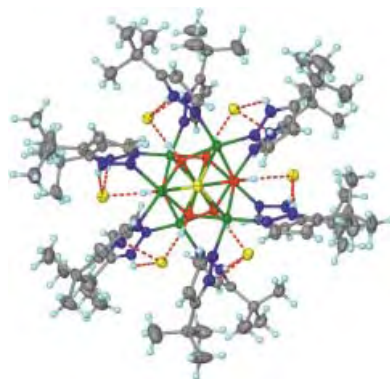
Angew. Chem. **2002**, *114*, 780–782

H. Birkedal,* D. Schwarzenbach,
P. Pattison 754–756

Observation of Uniaxial Negative
Thermal Expansion in an Organic Crystal

Keywords: crystal engineering • helical
structures • hydrogen bonds • peptides •
X-ray diffraction

An unusual vertex-shared double-cubane [$\text{Cu}_3(\mu_3\text{-Cl})(\mu_3\text{-OH})_3\text{Cu}]^{6+}$ core surrounded by a belt of hydrogen-bonded chloride ions is present in the title compound. Magnetic data show an $S = 1/2$ ground state, which implies there is substantial spin-frustration within the hepta-copper aggregate.



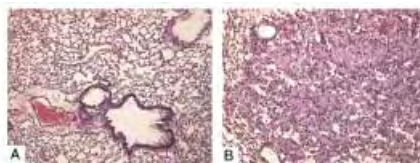
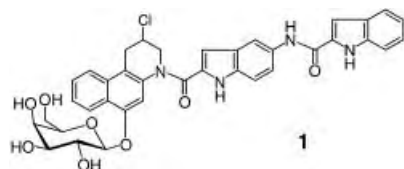
Angew. Chem. **2002**, *114*, 782–784

X. Liu, J. A. McAllister,
M. P. de Miranda, B. J. Whitaker,
C. A. Kilner, M. Thornton-Pett,
M. A. Halcrow* 756–758

Supramolecular Templating of the
Double-Cubane [$\text{Cu}_3(\text{Hpz}^{\text{tBu}})(\mu_3\text{-Cl})\text{-}$
 $(\mu_3\text{-OH})_3\text{Cu}] \text{Cl}_6$ ($\text{Hpz}^{\text{tBu}} = 5\text{-tert-}$
Butylpyrazole)

Keywords: cluster compounds • copper •
hydrogen bonds • magnetochemistry •
N ligands

Perfectly adept for tumor treatment: With the seco-CBI-Q galactoside **1** a novel highly potent prodrug for the selective treatment of cancer using the ADEPT approach was developed, which shows very promising results in preclinical trials on a human bronchial carcinoma in SCID mice (see picture; lung tissue after (A) and before treatment (B)).



Angew. Chem. **2002**, *114*, 785–787

L. F. Tietze,* T. Feuerstein, A. Fecher,
F. Haunert, O. Panknin, U. Borchers,
I. Schuberth, F. Alves 759–761

Proof of Principle in the Selective
Treatment of Cancer by Antibody-
Directed Enzyme Prodrug Therapy: The
Development of a Highly Potent Prodrug

Keywords: ADEPT • antitumor agents •
enzymes • glycosides • monoclonal
antibodies • prodrugs

α-Helical L- and D-polyalanines have magnetic properties when self-assembled as monolayers on gold surfaces. The properties depend on the chirality of the molecules and on the direction of their dipole moment relative to the substrate. They were investigated by IR spectroscopy, which determined the orientation of the molecules relative to the surface in the presence of a magnetic field, and by measuring the spin selectivity for electron transmission through the layers.

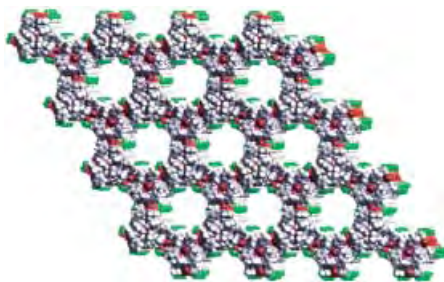
Angew. Chem. **2002**, *114*, 787–790

I. Carmeli, V. Skakalova, R. Naaman,*
Z. Vager 761–764

Magnetization of Chiral Monolayers of
Polypeptide: A Possible Source of
Magnetism in Some Biological
Membranes

Keywords: chirality • electron transport •
magnetic properties • monolayers •
peptides

No interpenetration: The use of bulky phosphane ligands allows the preparation of a non-interpenetrating two-dimensional nanoporous structure with hexagonal channels (see picture). In the as-synthesized polymer these channels are saturated with solvent, however, this solvent can be exchanged for other solvents which in turn can be removed by heating under vacuum without collapse of the structure.



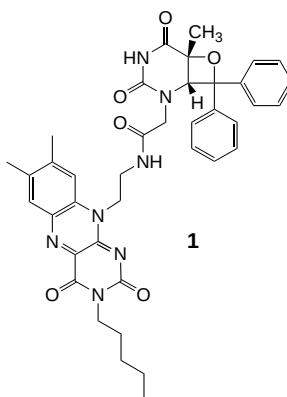
Angew. Chem. **2002**, *114*, 790–793

X. Xu, M. Nieuwenhuyzen,
S. L. James * 764–767

A Nanoporous Metal–Organic
Framework Based on Bulky Phosphane
Ligands

Keywords: crystal engineering •
host–guest systems • nanostructures •
phosphane ligands • polymerization •
silver

Photolyase-catalyzed repair of pyrimidine (6-4) photoadducts was modeled with synthetic, covalently linked flavin–oxetane **1**. The repair reaction (oxetane splitting) requires the reduced flavin in its deprotonated form. The key step of the repair reaction involves an electron transfer from the flavin to the oxetane.



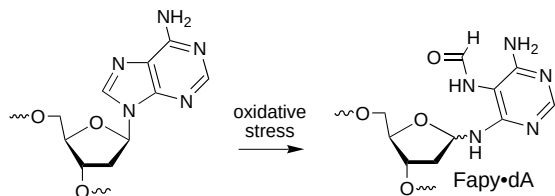
M. K. Cichon, S. Arnold,
T. Carell * 767–770

A (6-4) Photolyase Model: Repair of
DNA (6-4) Lesions Requires a Reduced
and Deprotonated Flavin

Keywords: bioorganic chemistry • DNA •
DNA repair • mutagenesis • photolyase

Angew. Chem. **2002**, *114*, 793–796

Formamidopyrimidine lesions (Fapy·dA; see scheme) are produced in greater yields than 8-oxopurines (OA) under O₂-deficient conditions from a common intermediate. OA give rise to low levels of A→C transversions. In vitro experiments show that Fapy·dA induces a DNA polymerase to misinsert nucleotides significantly more often than does OA, which suggests that the formamidopyrimidine may be a more potent premutagenic lesion.



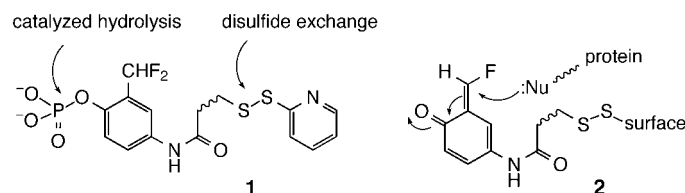
Angew. Chem. **2002**, *114*, 797–799

M. O. Delaney, C. J. Wiederholt,
M. M. Greenberg * 771–773

Fapy·dA Induces Nucleotide
Misincorporation Translesionally by a
DNA Polymerase

Keywords: bioorganic chemistry • DNA •
DNA damage • DNA polymerase •
mutagenesis

Disulfide exchange leads to the attachment of phosphate ester **1** to a solid surface, which can then be used in turnover selection to screen a large library of proteins for phosphate monoester hydrolysis activity. This ester hydrolysis leads to formation of an electrophilic quinone methide **2**, which bonds covalently to the protein catalyst and links it to the surface for selection.



Angew. Chem. **2002**, *114*, 801–803

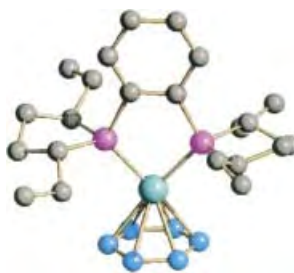
J. R. Betley, S. Cesaro-Tadic,
A. Mekhelfia, J. H. Rickard, H. Denham,
L. J. Partridge, A. Plückthun,*
G. M. Blackburn * 775–777

Direct Screening for Phosphatase Activity
by Turnover-Based Capture of Protein
Catalysts

Keywords: biosensors • catalytic
antibodies • enzyme catalysis •
inhibitors • phosphatases



Blocking the catalyst through the formation of $\text{Rh}^I-\eta^6\text{-arene}$ complexes (the complex $[\text{Rh}((R,R)\text{-Et-DuPHOS})(\text{C}_6\text{H}_6)]^+$ is shown; $\text{Et-DuPHOS} = 2',5',2'',5''\text{-tetraethyl-1,2-bis(phospholanyl)benzene}$) can decrease the activity of asymmetric hydrogenations. The inhibiting effects of aromatic compounds were quantified by means of kinetic measurements and confirmed by means of X-ray crystal structure analysis and ^{103}Rh NMR spectroscopy.



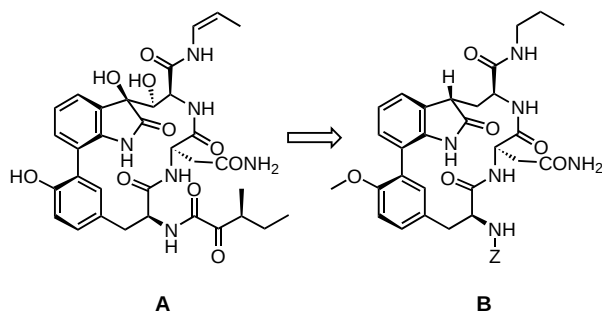
D. Heller,* H.-J. Drexler,
A. Spannenberg, B. Heller, J. You,
W. Baumann* 777–780

The Inhibiting Influence of Aromatic
Solvents on the Activity of Asymmetric
Hydrogenations

Keywords: arene ligands • asymmetric
catalysis • hydrogenation • NMR
spectroscopy • rhodium

Angew. Chem. **2002**, *114*, 814–817

Based on information from the X-ray structure of the TMC-95A/proteasome complex, TMC-95A (**A**) was reduced to the minimum core structure (**B**). The inhibitory potency of the synthetic analogue confirms that the simplified ring structure may well serve as the lead for further improvement of affinity and selectivity of reversible proteasome inhibitors.



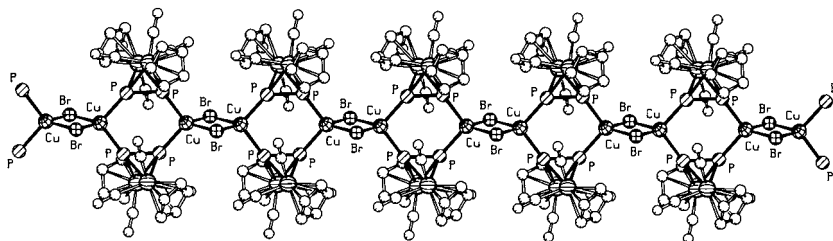
Angew. Chem. **2002**, *114*, 817–820

M. Kaiser, M. Groll, C. Renner,
R. Huber, L. Moroder* 780–783

The Core Structure of TMC-95A Is a
Promising Lead for Reversible
Proteasome Inhibition

Keywords: inhibitors • natural products •
NMR spectroscopy • structure–activity
relationships • total synthesis

Bridging coordination of Mo_2P_2 complexes between metal centers is a prerequisite for the formation of a one-dimensional polymer. The choice of counterion also has a deciding role in determining the polymer structure: while the complex $[\text{Cp}_2\text{Mo}_2(\text{CO})_4(\mu,\eta^2\text{-P}_2)]$ (**1**; $\text{Cp} = \text{C}_5\text{H}_5$) with AgNO_3 forms a zigzag polymer chain, with CuBr **1** forms a linear coordination polymer (see structure).



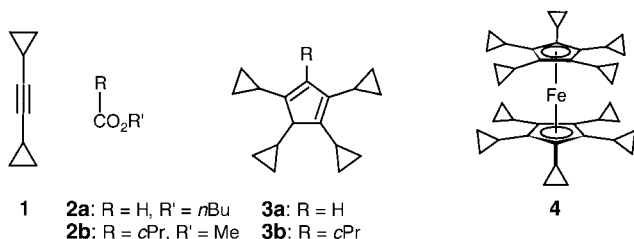
Angew. Chem. **2002**, *114*, 820–823

J. Bai, E. Leiner, M. Scheer* .. 783–786

P_2 -Ligand Complexes as Building Blocks
for the Formation of One-Dimensional
Polymers

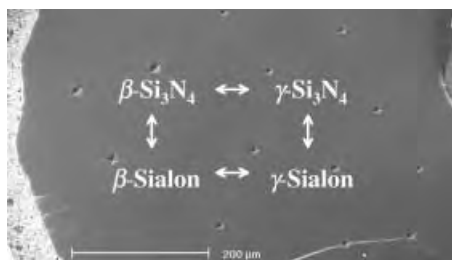
Keywords: coordination polymers •
copper • molybdenum • P ligands •
silver

 **Accessible in one step each**, tetra- and pentacyclopropylcyclopentadiene (**3**) can be prepared from dicyclopropylacetylene (**1**) and *n*-butyl formate (**2a**) or methyl cyclopropanecarboxylate (**2b**), respectively. The five cyclopropyl substituents in **3b** exert a significant donor effect on the cyclopentadienide core when this is bound to a metal center such as in **4**.



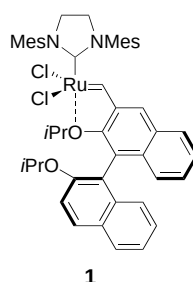
Angew. Chem. **2002**, *114*, 811–814

Excellent mechanical properties make γ - Si_2AlON_3 , one of the first spinel sialons and 4-3-spinels, a promising material for structural and abrasive applications. The hardness of this phase synthesized at 13 GPa/1800°C surpasses that of the low-pressure α - and β -sialons, which are used for metal-cutting and engineering applications. The picture shows a γ - Si_2AlON_3 surface that was used for Vickers hardness testing and indicates the structural relation between β - and γ -sialons and the corresponding phases of Si_3N_4 .



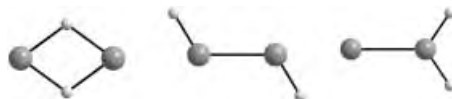
Angew. Chem. **2002**, *114*, 804–808

A bulky binol-based ligand is the key structural feature of the ruthenium complex **1**, which displays an unprecedented metathesis activity combined with high stability. For a range of dienes, ring-closing metathesis reactions catalyzed by **1** lead to near quantitative yields of cycloalkenes after a few minutes.



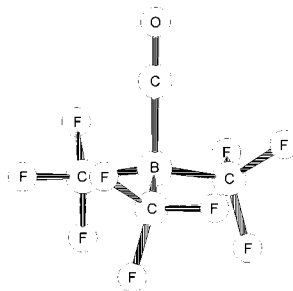
Angew. Chem. **2002**, *114*, 832–834

The five binary species $\text{Ga}(\mu\text{-H})_2\text{-Ga}$, $\text{In}(\mu\text{-H})_2\text{-In}$ (see left structure), HGaGaH , HInInH (center), and GaGaH_2 (right) were prepared by matrix isolation and characterized unambiguously by IR spectroscopy and quantum-chemical calculations. Investigations of the photochemical properties reveal that each of the isomers can be interconverted by photolysis.



Angew. Chem. **2002**, *114*, 829–832

By hydrolysis of a single CF_3 group in concentrated sulfuric acid, the new boron carbonyl $(\text{CF}_3)_3\text{B-CO}$ compound (see molecular structure) is obtained from $\text{K}[\text{B}(\text{CF}_3)_4]$. $(\text{CF}_3)_3\text{B-CO}$ exhibits rather unusual properties and bears an electrophilic carbonyl carbon atom.



Angew. Chem. **2002**, *114*, 823–825

I. Emme, S. Redlich, T. Labahn, J. Magull, A. de Meijere * 786–789

Tetra- and Pentacyclopropylcyclopentadiene—Two New Donor-Substituted Ligands for Metal Complexes

Keywords: carbocations • cyclopentadienyl ligands • hydrocarbons • metallocenes • substituent effects

M. Schwarz,* A. Zerr, E. Kroke,* G. Miehe, I.-W. Chen, M. Heck, B. Thybusch, B. T. Poe, R. Riedel 789–793

Spinel Sialons

Keywords: ceramics • high-pressure chemistry • oxide nitrides • sialons • spinel phases

H. Wakamatsu, S. Blechert * .. 794–796

A Highly Active and Air-Stable Ruthenium Complex for Olefin Metathesis

Keywords: biaryls • carbene ligands • metathesis • O ligands • ruthenium

H.-J. Himmel,* L. Manceron, A. J. Downs, P. Pullumbi 796–799

Characterization and Photochemistry of the Gallium and Indium Subhydrides Ga_2H_2 and In_2H_2

Keywords: gallium • hydrides • indium • matrix isolation • photochemistry

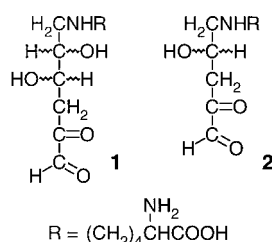
A. Terheiden, E. Bernhardt, H. Willner,* F. Aubke * 799–801

Carbonyltris(trifluoromethyl)borane, $(\text{CF}_3)_3\text{BCO}$, An Unusual Boron Carbonyl

Keywords: ab initio calculations • boranes • carbonyl ligands • IR spectroscopy



The novel dideoxyosones 1 and 2 were shown to be precursors of the important *in vivo* crosslinks glucosepane and pentosidine. In **1** and **2**, the lysine *N*^ε atom is directly bonded to C1 of the original sugar group. The formation of these compounds proceeds through carbonyl shifts along the entire carbohydrate backbone.



Angew. Chem. **2002**, *114*, 826–828

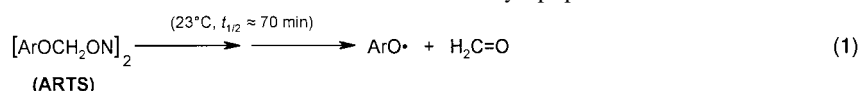
K. M. Biemel, J. Conrad,
M. O. Lederer* 801–804

Unexpected Carbonyl Mobility in
Aminoketoses: The Key to Major
Maillard Crosslinks

Keywords: carbohydrates • heterocycles •
Maillard reaction • protein cross-linking •
structure elucidation



ARTS in chemistry: Aryloxymethyl hyponitrites provide the first aryloxy radical thermal sources (**ARTS**) which generate a well-defined flux of aryloxy radicals ($ArO^\bullet$) at room temperature [Eq. (1)]. These novel compounds can be used for quantitative studies on reactions of $ArO^\bullet$ with biomolecules, as exemplified by the $PhO^\bullet$ -mediated oxidation of human low-density lipoprotein.



Angew. Chem. **2002**, *114*, 808–811

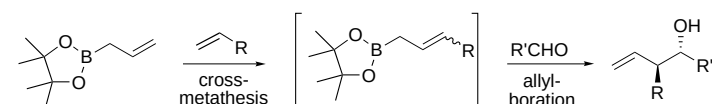
T. Paul,* K. U. Ingold* 804–806

A Method for Thermal Generation of
Aryloxy Radicals at Ambient
Temperatures: Application to Low-
Density Lipoprotein (LDL) Oxidation

Keywords: azo compounds •
lipoproteins • oxidation • radicals •
vitamins



Reactive reagents can be prepared by means of olefin cross-metathesis. A wide variety of functionalized allyl boronates were synthesized and were found to react cleanly with aldehydes to afford homoallylic alcohols, without prior purification (see scheme). Olefins that bear allylic ethers, halides, protected aldehydes, and sterically encumbering groups are viable substrates for this reaction.



Angew. Chem. **2002**, *114*, 835–838

S. D. Goldberg, R. H. Grubbs* 807–810

A One-Pot Cross-Metathesis/
Allylboration Reaction: A Three-
Component Coupling for the Synthesis of
Functionalized Homoallylic Alcohols

Keywords: allylation • boranes •
chemoselectivity • cross-coupling •
metathesis

When four conditions are met redox polymers can be electrodeposited by ligand exchange: the film must be electron- or hole-conducting; the redox centers of the deposited polymer that are based on transition metal complexes must contain a labile ligand in their inner coordination sphere; the redox polymer must contain a strongly coordinating but yet uncoordinated ligand; and the surface density of the adsorbed redox polymer must be high. By taking care of these points, the authors also succeeded in co-depositing enzymes and electroreducing/oxidizing their substrates with the electrodes obtained.

Angew. Chem. **2002**, *114*, 838–841

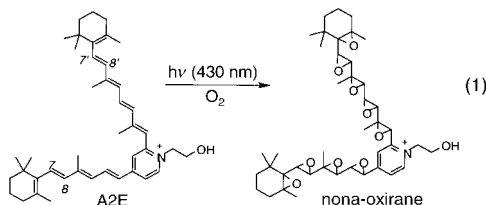
Z. Gao, G. Binyamin, H.-H. Kim,
S. C. Barton, Y. Zhang,
A. Heller* 810–813

Electrodeposition of Redox Polymers and
Co-Electrodeposition of Enzymes by
Coordinative Crosslinking

Keywords: biosensors • chelates •
electrochemistry • polymerization •
redox chemistry



Nine epoxide rings are formed sequentially when A2E is irradiated with blue light in the presence of oxygen [Eq. (1)]. Mechanistically, A2E generates singlet oxygen and reacts with it to give the polyoxiranes. An understanding of the reaction of A2E with oxygen is important as blue light induces the apoptotic death of A2E-laden retinal pigment epithelium cells, which are typical of age-related macular degeneration.



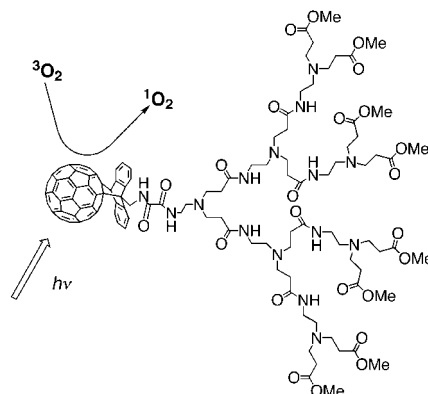
S. Ben-Shabat, Y. Itagaki, S. Jockusch,
J. R. Sparrow,* N. J. Turro,*
K. Nakanishi* 814–817

Formation of a Nona-oxirane from A2E,
a Lipofuscin Fluorophore related to
Macular Degeneration, and Evidence of
Singlet Oxygen Involvement

Keywords: heterocycles • macular
degeneration • peroxides •
photochemistry • singlet oxygen

Angew. Chem. **2002**, *114*, 842–845

Reversible Diels–Alder reaction of C₆₀ with an anthracenyl dendron bearing a poly(amidoamine) substituent forms the fullerodendrimer depicted. It is readily soluble in water and acts as a photosensitizer for the generation of singlet oxygen.



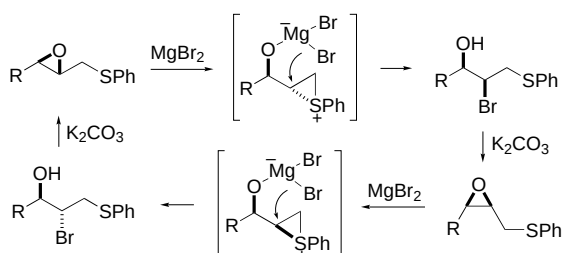
Angew. Chem. **2002**, *114*, 845–847

Y. Takaguchi,* T. Tajima, K. Ohta, J. Motoyoshiya, H. Aoyama, T. Wakahara, T. Akasaka,* M. Fujitsuka, O. Ito* 817–819

Reversible Binding of C₆₀ to an Anthracene Bearing a Dendritic Poly(amidoamine) Substituent to give a Water-Soluble Fullerodendrimer

Keywords: cycloaddition • dendrimers • fullerenes • photochemistry • singlet oxygen

A double inversion of configuration and episulfonium ion intermediates are at the heart of a method for the stereospecific interconversion between *cis* and *trans* 2,3-epoxysulfides (see scheme). This method can be used in the stereoselective synthesis of epoxides.



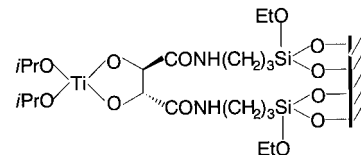
Angew. Chem. **2002**, *114*, 847–849

A. Hirai, T. Tonooka, K. Wakatsuki, K. Tanino, M. Miyashita* 819–821

Stereospecific Interconversion between *cis* and *trans* 2,3-Epoxysulfides

Keywords: bromohydrins • epoxidation • isomerization • nucleophilic substitution • synthetic methods

A heterogeneous version of the Sharpless epoxidation: a chiral tartaric acid derivative is grafted onto the surface of silica and in the mesopores of MCM-41 (see picture). The hybrid chiral catalyst is as effective as the homogeneous complex in terms of turnover number and enantioselectivity, and the product is easily separated by simple filtration.



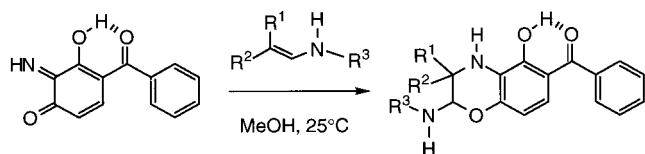
Angew. Chem. **2002**, *114*, 849–852

S. Xiang, Y. Zhang, Q. Xin, C. Li* 821–824

Asymmetric Epoxidation of Allyl Alcohol on Organic–Inorganic Hybrid Chiral Catalysts Grafted onto the Surface of Silica and in the Mesopores of MCM-41

Keywords: alcohols • allylic compounds • asymmetric catalysis • epoxidation • heterogeneous catalysis • synthetic methods

The regiospecific cycloaddition of an *o*-quinone imine and a highly reactive enamine, which are electrogenerated simultaneously, can be carried out at ambient temperature in the absence of catalyst. This reaction is a powerful tool for the one-pot synthesis of new polyfunctionalized 1,4-benzoxazine derivatives (see scheme).



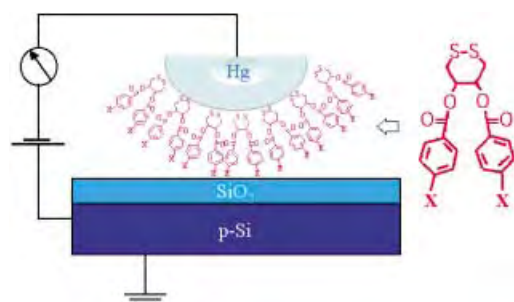
Angew. Chem. **2002**, *114*, 852–855

M. Largeron,* A. Neudorffer, M. Vuilhorgne, E. Blattes, M.-B. Fleury 824–827

Regiospecific Inverse-Electron-Demand Diels–Alder Reaction of Simultaneously Electrogenerated Diene and Dienophile: An Expeditious Route to Polyfunctionalized 1,4-Benzoxazine Derivatives

Keywords: cofactors • cycloaddition • electrochemistry • nitrogen heterocycles • quinones • synthetic methods

Junction function: Molecule-controlled devices based on metal–semiconductor junctions can exhibit negative differential resistance (NDR) at room temperature. The active component is a self-assembled monolayer of molecular dipoles (see schematic representation; X = CF₃, CN, H, OMe). A systematic change in the dipole moment of these molecules results in a corresponding systematic change in the NDR effect, thus establishing for the first time molecularly tunable NDR.



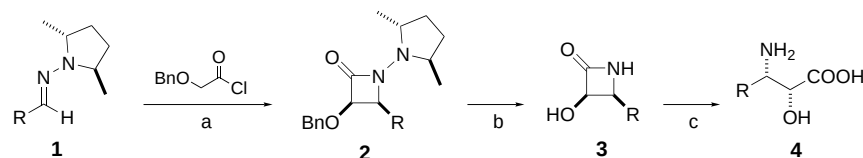
Angew. Chem. **2002**, *114*, 855–858

Y. Selzer,* A. Salomon, J. Ghabboun,
D. Cahen * 827–830

Voltage-Driven Changes in Molecular
Dipoles Yield Negative Differential
Resistance at Room Temperature

Keywords: mercury • molecular devices •
monolayers • self-assembly •
semiconductors • Umpolung

To overcome the limitations of using unstable imines in Staudinger cycloadditions to ketenes, aldehyde *N,N*-dialkylhydrazones **1** were used as stable imines. This strategy and a fine tuning of the auxiliary result in a straightforward synthesis of cycloadducts **2**, deprotected β -lactams **3**, and isoserines **4** (see scheme: a) Et₃N, toluene, Δ ; b) 1. magnesium monoperoxyphthalate, 2. H₂, Pd/C; c) H⁺).



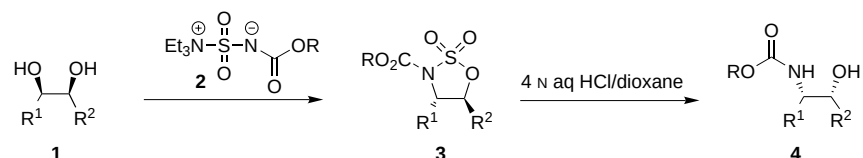
Angew. Chem. **2002**, *114*, 859–861

R. Fernández, A. Ferrete,
J. M. Lassaletta,* J. M. Llera,*
E. Martín-Zamora 831–833

N,N-Dialkylhydrazones as the Imine
Component in the Staudinger-Like [2+2]
Cycloaddition to Benzyloxyketene

Keywords: asymmetric synthesis •
cycloaddition • hydrazones • lactams •
synthetic methods

An increasingly targeted functional motif in organic synthesis is the ubiquitous chiral β -amino alcohol. A novel two-step approach for the regio- and stereo-selective synthesis of a wide variety of 1,2-amino alcohols **4** involves the initial construction of chiral sulfamidates **3** from enantiopure diols **1**, mediated by Burgess reagent (**2**, R = Me), followed by mild treatment with aqueous acid. Furthermore, the development of several new Burgess-type reagents (**2** (R = CH₂Ph, CH₂-*o*-NO₂Ph, CH₂CHCH₂, CH₂CCl₃) greatly extends the applications of this protocol.



Angew. Chem. **2002**, *114*, 862–866

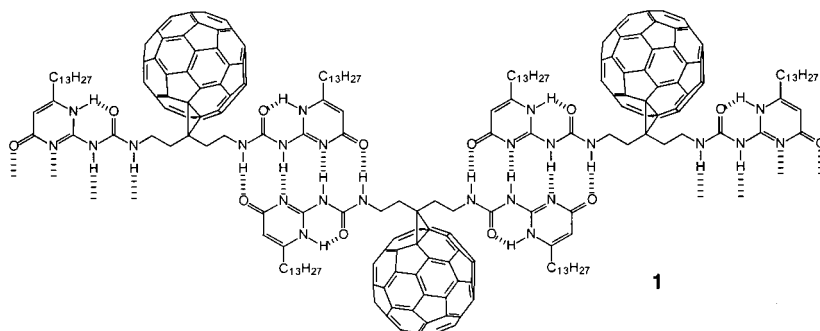
K. C. Nicolaou,* X. Huang, S. A. Snyder,
P. Bheema Rao, M. Bella,
M. V. Reddy 834–838

A Novel Regio- and Stereoselective
Synthesis of Sulfamidates from 1,2-Diols
Using Burgess and Related Reagents:
A Facile Entry into β -Amino Alcohols

Keywords: amino alcohols • asymmetric
synthesis • Burgess reagents •
sulfamidates • synthetic methods



Bucky balls and chains: The quadruple hydrogen-bonded fullerene array **1** was synthesized and fully characterized. In the highly dynamic polymeric state, the chemical integrity of the monomeric moiety is fully preserved, also with respect to its redox and UV/Vis behavior. Hence, **1** can potentially serve as a building block in supramolecular electronics.



Angew. Chem. **2002**, *114*, 866–868

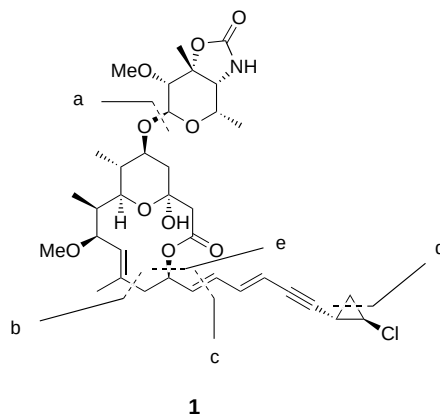
L. Sánchez, M. T. Rispens,
J. C. Hummelen* 838–840

A Supramolecular Array of Fullerenes by
Quadruple Hydrogen Bonding

Keywords: cyclic voltammetry •
fullerenes • hydrogen bonds • polymers •
supramolecular chemistry



A series of highly stereospecific reactions were used in the total synthesis of callipeltoside A (**1**), thus allowing the assignment of its absolute and relative configuration. a) Schmidt glycosylation, b) Ru Alder–ene coupling, c) Emmons–Wadsworth–Horner olefination, d) chiral auxiliary directed alkylation, e) asymmetric allylic Pd alkylation.



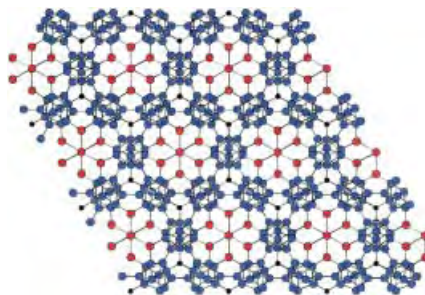
Angew. Chem. **2002**, *114*, 869–871

B. M. Trost,* O. Dirat,
J. L. Gunzner 841–843

Callipeltoside A: Assignment of Absolute
and Relative Configuration by Total
Synthesis

Keywords: asymmetric synthesis •
configuration determination •
natural products • total synthesis

Synthesis in molten gallium provides access to a new class of boron-rich quaternary phases. Its first member, $\text{Tb}_{1.8}\text{C}_2\text{Si}_8(\text{B}_{12})_3$, represents a new structure type in which B_{12} icosahedra, eight Si atoms in a staggered ethane-like arrangement, and C_2 units are interconnected (see picture; red: Si, blue: B, black: C). The Tb sites have a partial occupation of about 60%.



Angew. Chem. **2002**, *114*, 872–874

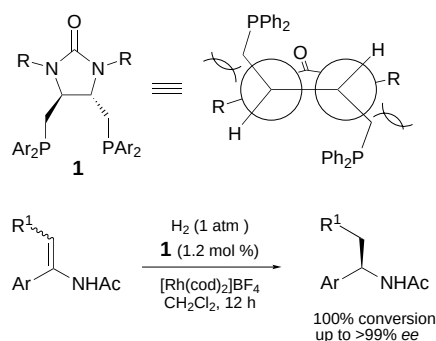
J. R. Salvador, D. Bile, S. D. Mahanti,
M. G. Kanatzidis* 844–846

Gallium Flux Synthesis of
 $\text{Tb}_{3-x}\text{C}_2\text{Si}_8(\text{B}_{12})_3$: A Novel Quaternary
Boron-Rich Phase Containing B_{12}
Icosahedra

Keywords: boron • gallium • high-
temperature chemistry • lanthanides •
silicon



Appropriate *gauche* steric interactions between the N-substituents and the phosphanylmethyl groups (see picture, top right) in the novel 1,4-diphosphane ligands **1** having an imidazolidin-2-one backbone affect the conformational flexibility of the seven-membered chelate ring formed by coordination to a metal atom. Thus, Rh complexes of **1** are excellent catalysts for enantioselective hydrogenation of enamides (bottom, cod = cycloocta-1,5-diene).



S.-g. Lee,* Y. J. Zhang, C. E. Song,
J. K. Lee, J. H. Choi 847–849

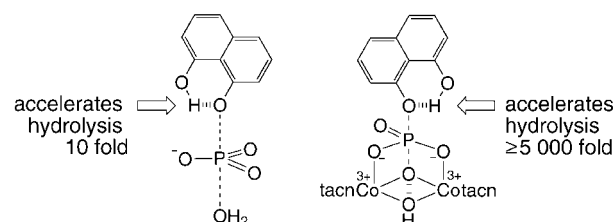
Novel 1,4-Diphosphanes with
Imidazolidin-2-one Backbones as Chiral
Ligands: Highly Enantioselective Rh-
Catalyzed Hydrogenation of Enamides

Keywords: asymmetric catalysis •
hydrogenation • P ligands • rhodium

Angew. Chem. **2002**, *114*, 875–877



An intramolecular OH group can become much more effective in promoting phosphate hydrolysis when combined with multiple interactions in a model for the metallophosphatase active site (see picture; tacn = 1,4,7-triazacyclononane).



M. Forconi, N. H. Williams* .. 849–852

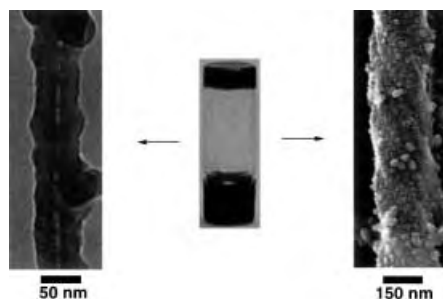
Mimicking Metallophosphatases:
Revealing a Role for an OH Group with
No Libido

Keywords: cooperative effects • enzyme
models • hydrolysis • metalloenzymes

Angew. Chem. **2002**, *114*, 877–880



Elaborate transcription of unimolecular stacks or helically bundled fibers of sugar-appended porphyrin gelators into silica by sol–gel polycondensation of tetraethoxysilane gives unique hollow silica fibers with a monodispersed 4-nm inner diameter (left picture) and huge helical silica bundles (right picture), respectively.



S.-i. Tamaru, M. Takeuchi, M. Sano,
S. Shinkai* 853–856

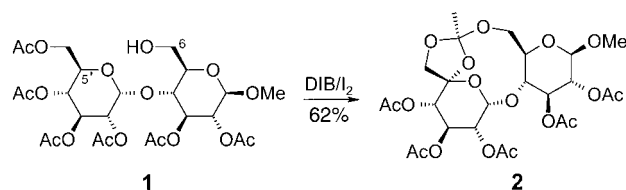
Sol–Gel Transcription of Sugar-
Appended Porphyrin Assemblies into
Fibrous Silica: Unimolecular Stacks
versus Helical Bundles as Templates

Keywords: organogel • porphyrinoids •
self-assembly • silicates • sol–gel
processes

Angew. Chem. **2002**, *114*, 881–884



A nine-membered transition state characterizes the regioselective abstraction of the proton at C₅ that leads to the orthoacetate **2** as the product. The alkoxy radical intermediate is obtained from the Glc- α 1 $\rightarrow$ 4-Glc derivative **1** with (diacetoxy-iodo)benzene (DIB) and iodine. A similar 1,8-hydrogen abstraction results when the alkoxy radical intermediate is generated under reductive conditions.



C. G. Francisco, A. J. Herrera,
A. R. Kennedy, D. Melián,
E. Suárez* 856–858

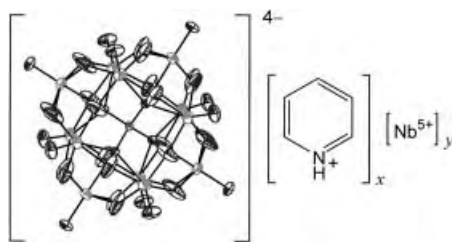
Intramolecular 1,8-Hydrogen Abstraction
Between Glucopyranose Units in a
Disaccharide Model Promoted by Alkoxy
Radicals

Keywords: carbohydrates • conformation
analysis • glycosides • hydrogen
transfer • radical reactions

Angew. Chem. **2002**, *114*, 884–886



A niobium and pyridine salt of molybdo(vanado)phosphoric acid (see formula) leads to a catalyst that achieves excellent yield and productivity for both the conversion of propane into acrylic acid and *n*-butane into maleic acid. The catalyst is active under either hydrocarbon-rich or -lean reaction conditions.



M. E. Davis,* C. J. Dillon, J. H. Holles, J. Labinger 858–860

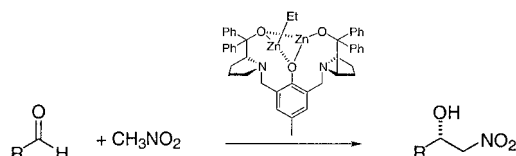
A New Catalyst for the Selective Oxidation of Butane and Propane

Keywords: alkanes • carbonyl compounds • heterogeneous catalysis • oxidation • polyoxometalates

Angew. Chem. **2002**, *114*, 886–888



A high level of enantioselectivity (78–93 % *ee*) and high yields (58–90 %) are obtained in the enantioselective nitroaldol reaction of nitromethane with several aldehydes when a novel dinuclear zinc catalyst is employed (see scheme).



Angew. Chem. **2002**, *114*, 889–891

B. M. Trost,* V. S. C. Yeh 861–863

A Dinuclear Zn Catalyst for the Asymmetric Nitroaldol (Henry) Reaction

Keywords: asymmetric catalysis • chiral ligands • nitroaldol reaction • zinc



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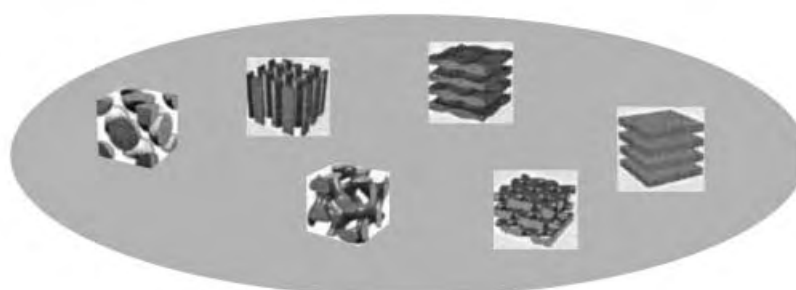
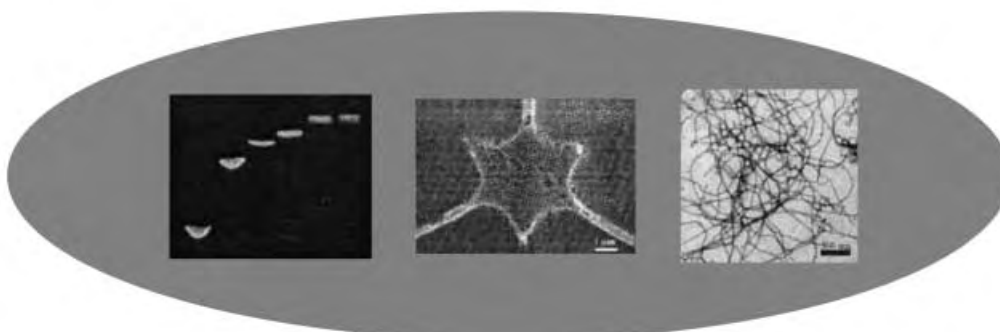
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Functional structural hierarchies from self-organizing polymers



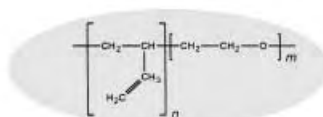
μm



nm



$\text{\AA}$



From Self-Organizing Polymers to Nanohybrid and Biomaterials

Stephan Förster* and Thomas Plantenberg

Block copolymers form a large number of superlattices with characteristic dimensions in the range of a few nanometers up to several micrometers by self-organization. The interplay of supramolecular physics and chemistry opens up new approaches to the production of inorganic, organic, and bio-

logical structures and to their integration into functional units. Possible applications in the fields of materials science and molecular biology are being investigated. Block copolymers find numerous applications from the production of inorganic nanoparticles (metals, semiconductors, magnets) and

mesoporous materials up to take-up/release systems in chemo- and gene therapy.

Keywords: amphiphiles • hybrid materials • nanostructures • polymers • self-organization

1. Introduction

Today's materials science deals increasingly with nanostructures, that is, with structures of characteristic dimensions between 1 and 100 nm. This range is called the mesoscopic range as it is located between the microscopic range of atoms and molecules and the macroscopic range of solids. With lithography and etching processes, solid-state physics and electronics advance towards the field of nanostructures ("top-down" approach). A 1-GB chip, for example, is made with structures with a characteristic dimension of about 200 nm. Much smaller structures cannot be made with lithographic techniques because of the strong UV absorption of the coatings. Nature may serve as a model for the building-up of smaller structures. Here individual molecules are integrated into larger functional units and structural hierarchies by self-organization and the building-up of compartments ("bottom-up" approach). One of the great challenges facing physics, chemistry, and materials science today is to find a way to structure molecules so as to enable them to build functional superlattices by self-organization.

The aim of this review is to give a survey of the fundamental principles of self-organization recently developed, particularly in macromolecular chemistry, and applied to materials science. The close link between "supramolecular chemistry" and "supramolecular physics" is also shown. The compounds discussed are mostly molecules of simple chemical structure

which, as a result of self-organization, can build up a wide variety of superstructures. A chemical functionalization can be achieved on every level of a structural hierarchy and results in functional materials in catalysis, electro-optics, high-performance ceramics as well as chemo- and gene therapy. Inorganic, organic, and biological materials can be integrated into functional systems. It is often necessary to bring together top-down and bottom-up strategies in order to realize structures with lengths ranging over several orders of magnitude.

2. Self-Organization

Whereas technical systems are organized by technicians, many natural systems organize themselves by internal processes. Order by self-organization is a phenomenon which has fascinated scientists of many different fields of research.

A wide variety of phenomena are regarded as self-organization in the various scientific disciplines, and the definitions applied differ. The following selection is taken from the relevant literature:^[1-3]

- Chemistry: Self-organization = well-defined structures result spontaneously from the components of a system by noncovalent forces (self-assembly), for example, in liquid crystals, micelles, oscillating reactions.
- Biology: Self-organization = a spontaneous building-up of complex structures which takes place under adequate environmental conditions solely on the basis of the respective molecular property, namely, without the effect of external factors, for example, protein folding, formation of lipid double layers, morphogenesis.

[*] Prof. Dr. S. Förster, Dipl.-Chem. T. Plantenberg
Institute für Physikalische Chemie
Universität Hamburg
Bundesstrasse 45, 20146 Hamburg
Fax: (+49) 40-42838-3452
E-mail: forster@chemie.uni-hamburg.de

- Physics: Self-organization = spontaneous formation of new three-dimensional and temporal structures in complex systems which results from the cooperative effect of partial systems, for example, ferromagnetism, superconductivity, convection cells.

Furthermore the different steps in the evolution of matter from the development of the universe up to the formation of biological macromolecules and to the origin of life are understood as a chain of fundamental processes of self-organization.

In spite of the diversity of the phenomena observed, there is a fundamental common feature. They share the fact that in the course of self-organization a system produces properties (for example, order) it did not have before. This development can be described by the theory of spontaneous symmetry breaking.^[3] An isotropic homogeneous system has a high symmetry, that is, there are a lot of symmetry operations (for example, rotations, reflections) which transform the system in itself. When the system passes from an isotropic to an oriented state, symmetry elements get lost – the symmetry is broken. Symmetry breaking is always followed by a new system property. This is shown by the equation of state of the system containing a new additional variable, the order parameter. The latter describes the degree of orientation or order of a system. The theory not only describes in general terms the fact that new properties develop, but moreover, explains what kind of properties emerge and how they develop.

In regard to materials science, we have to distinguish between equilibrium systems (for example, liquid crystals, lipid double layers, ferromagnetism) and nonequilibrium systems (for example, convection cells, oscillating reactions). In equilibrium systems symmetry breaking is associated with a phase transition, and in nonequilibrium systems with a dynamic instability. In systems far away from thermodynamic equilibrium, dynamic instabilities result in the formation of ordered, so-called dissipative structures. In the case of turbulence or convection, for example, the formation of

regular convection cells (Bénard cells) or rotational vortices (Taylor vortices) is observed. Whereas equilibrium systems reach a stable state after phase transition, dissipative structures are instable and develop towards increasingly more complex and chaotic states. These are very fascinating and represent the object of many observations about morphogenesis and the origin of life. They are, however, not very suitable for materials structuring. Therefore they will not be dealt with in the following discussion.

2.1. Principles of Self-Organization

The transition from a disordered to an ordered state by spontaneous symmetry breaking can be described by an order parameter η which indicates the degree of order of the phase. From the definition, the order parameter is $\eta = 0$ in the disordered phase, it deviates from zero when symmetry breaking and the transition to the ordered phase take place, and reaches the value $\eta = 1$ in the ideal, ordered phase. This definition has proved to be useful for describing order processes in the field of condensed matter such as fluid crystals, ferromagnets, ferroelectrics, superconductors, and superfluids.

The transition from a disordered into an ordered phase takes place by changing thermodynamic or physical field strength. Such changes may be those of temperature and chemical potential (concentration, pH value, salt addition), of mechanical fields (pressure, shear, extension, ultrasonics), as well as of electric and magnetic fields. Systems which react to the change of field strength by a phase transition and hence by an abrupt change of a particular property, are called actuators. They play an important role in many pharmacological applications where active ingredients can be released purposefully by changing the salt concentration, pH value, temperature, or by applying ultrasound (see Section 5).

Stephan Förster studied chemistry at the University of Mainz and the University of Toronto (Canada). He completed his diploma and Ph.D. under the supervision of Prof. G. Wegner and Prof. M. Schmidt at the Max-Planck-Institute for Polymer Research, Mainz, Germany. He then went to the University of Minnesota, Minneapolis, USA, to work with Prof. F. S. Bates. In 1993, he joined the Max-Planck-Institute for Colloid and Interface Research in Teltow/Golm (Germany), where he led a project in Prof. M. Antonietti's group. In 1998 he was awarded the Dr. Hermann – Schnell prize by the Gesellschaft Deutscher Chemiker. In 1999 he completed his habilitation at the University of Potsdam (Germany) and took the chair of Physical Chemistry at the University of Hamburg.



S. Förster



T. Plantenberg

Thomas Plantenberg studied at the Universities of Köln and Potsdam (Germany). He completed his degree dissertation on polyelectrolytes under the supervision of Prof. J. Kötz at the University of Potsdam. He is presently completing his Ph.D. on polyelectrolyte micelles at the University of Hamburg in the group of Prof. Förster.

The ordered state is distinguished by the fact that individual molecules are located at restricted three-dimensional regions, for example, a lattice site in a crystal or the position in the three-dimensional structure of a protein. A localization is always accompanied by a decrease of the number of realizable states and hence a loss of entropy. Temperature plays always an important role in the case of phase transitions between different order states because of the contribution $T\Delta S$ to the free energy. Besides temperature, further external fields E may influence the degree of order and the phase transitions.

The field strength and temperature at which the phase transitions take place can be depicted schematically in phase diagrams (Figure 1). The critical temperature T_c above which

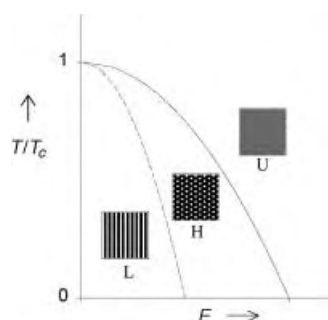


Figure 1. Transition from a disordered phase (U) to ordered phases (H, L) by variation of the temperature T and the external field E . T_c is the critical temperature above which ordered phases are not accessible. The transition $U \rightarrow H, L$ corresponds to a self-organization.

the system is disordered is indicated on the temperature axis. Phase transitions from the disordered phase (U) to different ordered phases (L, H) may take place below the critical temperature. These phase transitions are accompanied by a self-organization of the system. The stability range of the different phases can be taken from the phase diagram. Different ordered structures for one and the same material can be produced by varying the temperature and field strength. This variability has a favorable effect on the production and optimization of materials.

The phases L and H in Figure 1 are examples of systems with three-dimensionally modulated order parameters $\eta(x)$. In simple cases this can be described by a sine function $\eta(x) = \eta_0 \sin(2\pi x/d)$. η_0 represents the amplitude of the order parameter and d the periodic length, that is, the linear scale of this profile. The structures in Figure 1 were produced by a superposition of such sine functions.^[4] Such an order parameter $\eta(x)$ describes the three-dimensional distribution of two states A and B in a binary state system. It can be a pair of spin states ($\uparrow \downarrow$, ferromagnetism), of electric polarization ($+-$, ferroelectricity), or of the three-dimensional distribution of molecules A and B in liquid crystalline systems.

Not only is the specific production of different modulated structures of interest, but also the variation of the linear scale d . In the mesoscopic range, namely, $1 < d < 100$ nm, materials properties such as band gap, catalytic activity, porosity, immune response, or endocy-

tosis can decisively depend on this length scale. In simple systems as described below, this length scale can be controlled by the molecule size.

2.2. Molecular Prerequisites

In order to build up ordered structures it is indispensable that both long range repulsive and short range attractive forces exist at the same time (shown schematically in Figure 2). There are long-range repulsive interactions between the A and B regions. As a consequence of short-range attractive interactions (bond), however, both regions cannot move away from one another. When as many A/B pairs as possible but with as few A/B contacts as possible are to be distributed in space, it is advantageous to choose the configuration shown in Figure 2 for the A and B domains. Such a formation of ordered domains illustrates the principle of self-organization on the basis of attractive/repulsive pairs of forces.

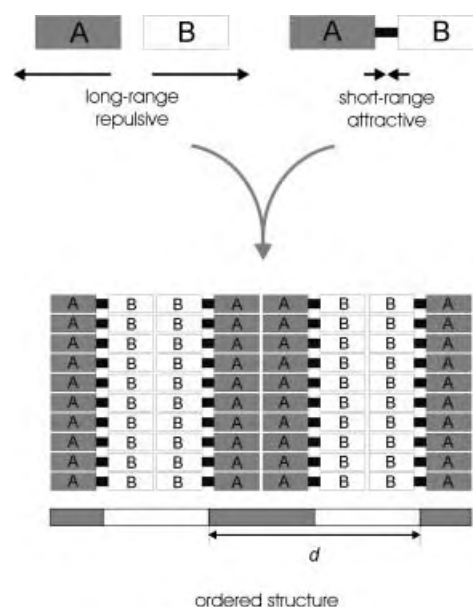


Figure 2. Illustration of long-range repulsive and short-range attractive forces leading to an ordered structure by self-organization (d is the periodic length of the structure).

Examples of such pairs of forces which are important for the formation of ordered materials are summarized in Table 1. Attractive interactions can be covalent bonds or the local conservation of electroneutrality. Repulsive interactions include the incompatibility of polymers, hydrophobic interac-

Table 1. Examples of pairs of forces which can lead to self-organization.

Long-range repulsion	Short-range attraction	Examples
hydrophilic/hydrophobic incompatibility	covalent binding	micelles, lyotropic liquid crystals
Coulombic repulsion	covalent binding	block copolymers
excluded volume	electroneutrality	ionic crystals
electric dipole field	minimum space required	thermotropic liquid crystals
magnetic field	electric dipole interaction	ferroelectric domains
	magnetic dipole interaction	magnetic domains

tions, and the excluded volume of formisotropic molecules. If there are several pairs of forces in the ordered structure of a system at the same time, these systems are called “frustrated” ones. They are characterized by a distinctive variety of ordered phases (polymorphism).

The formation of very similar, ordered structures (A and B domains) in such different materials as magnets, block copolymers, and liquid crystals (Figure 3),^[5] is a clear sign of the universality of this principle of self-organization. The structures only differ in their periodic length d , which covers a range from 10 nm to 1 cm, hence seven orders of magnitude.

When the formation of ordered structures can be expected, as a result of an appropriate pair of forces, the question arises as to which kind and periodicity the superlattice will be. The

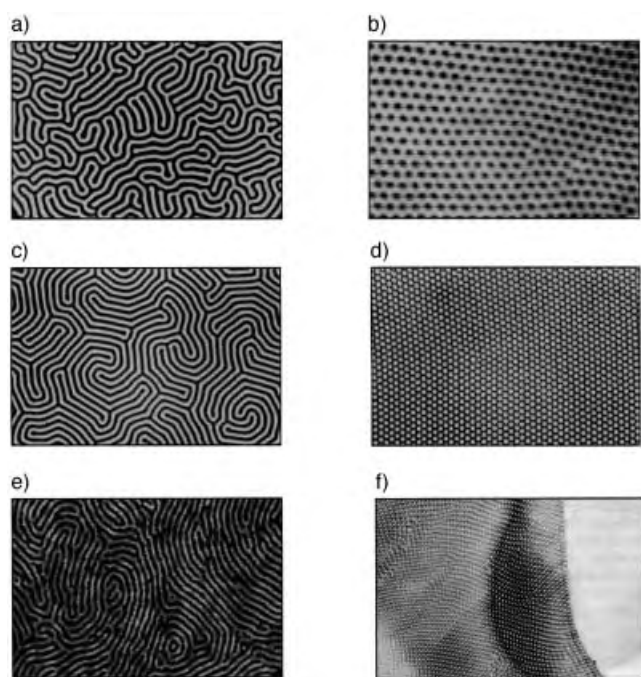


Figure 3. Lamellar (left) and hexagonal domains (right) in a ferrofluid with a) $d = 1$ cm, b) $d = 4$ μm , in a ferromagnetic film with c,d) $d = 10$ μm , and in a block copolymer superlattice with e) $d = 40$ nm, f) $d = 16$ nm. The examples give evidence of the universality of the order principles through pairs of forces. (From ref. [5].)

molecule subject to the interaction of the pair of forces, will join other molecules in such a way that domains and interfaces are formed which reflect the shape of the molecule. Figure 4 uses the example of Figure 2 once more. The A and B domains are separated from each other by an interface (dotted line). Planar interfaces are formed preferably because of the stretched shape of an A/B pair, and hence stripe or lamellar domains result. The periodic length d of the superlattice results from the size of the A and B domains.

When the B domain is smaller than the A domain, there will be curved interfaces. The bend can be characterized by the curvature radius R (Figure 4). It is not readily apparent with curved interfaces what will be the topology of the domains of the superlattice. By means of differential geometry it is, however, possible to predict the topologies and symmetries of the superlattices from the given curvature and

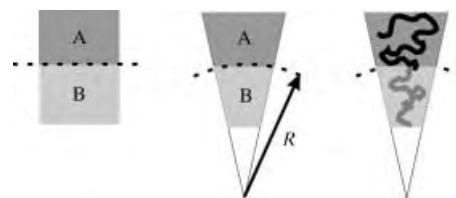


Figure 4. Local geometry and the curvature of domains and interfaces. The kind of superlattice depends on the volume ratio $f = V_A/V_B$ of the domains and on the curvature radius R of the interface. For a planar interface $R = \infty$. The application of this model to block copolymers is shown at the right hand side.

domain size. These do not only contain the classical superlattices of spheres, cylinders, and lamellae, but also complicated minimal surfaces such as G (gyroid), P (plumbers nightmare), or D surfaces (double diamond). These ones consist of bicontinuous, branched domains of cubic symmetry. As a consequence of their bicontinuous structure, they are of interest as materials for separation processes.

The free energy of a superlattice can be calculated by means of self-consistent mean field theory. The superlattice with the lowest energy conforms to the equilibrium structure, the stability range of which can be represented in a phase diagram (Figure 5).^[6] The product χN is plotted on the ordinate. N is the total degree of polymerization of the block copolymer

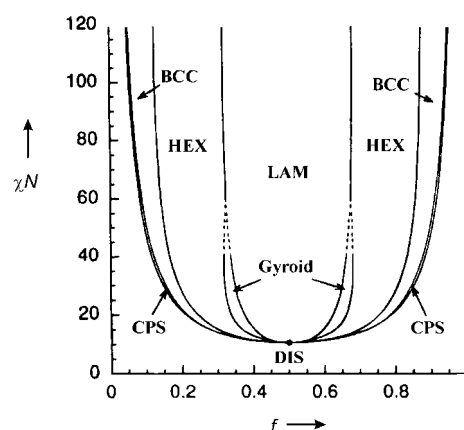


Figure 5. Theoretical phase diagram of block copolymers. Various ordered superlattices can be obtained by variation of the block lengths (f -axis) and the temperature (χN -axis; see the legend to Figure 13 for an explanation of the abbreviations). (From ref. [6].)

which results from the sum of the degrees of polymerization of the different blocks, namely, $N = N_A + N_B$. χ is the Flory–Huggins interaction parameter which indicates the strength of the repulsive interaction between both polymer blocks. The value of χ decreases with increasing temperature according to $\chi \sim 1/T$. Therefore this phase diagram seems to be turned upside down compared to the schematic phase diagram in Figure 1. f is the block length ratio ($f = N_A/N$) and, as a geometric factor, decides on the symmetry of the superlattice. By making use of such a phase diagram it is possible to purposefully produce different superlattices by varying the block lengths.

3. Block Copolymers

Macromolecules are particularly well suited for implementing physical, chemical, and biological functions at the same time. Nature demonstrates this with innumerable examples of biopolymers. Polymers permit the length scales to be greatly varied, the superstructure to be controlled, and specific functions to be performed. The simplest primary structure which permits these functions to be carried out are AB block copolymers. The last few years have seen considerable progress in the development of methods to synthesize block polymers, some of them applicable on an industrial scale.

3.1. Synthesis

3.1.1. Living Polymerization Techniques

During the last decade more and more advanced techniques of “living” or controlled polymerization to prepare block copolymers have become available. It has become possible to prepare block copolymers of various architectures, solubility, and functionality.^[7] Architectures comprise diblock, triblock, and multiblock copolymers arranged linearly as stars or grafts. The solubilities vary from polar solvents such as water to media with very low cohesion energies such as silicon oil or fluorinated solvents. Control of functionality has become important, motivated by the necessity to stabilize metallic, semiconductor, ceramic, or biological systems.

The different synthetic routes to block copolymers comprise living anionic, living cationic, and living radical polymerization. Combining different polymerization techniques provides a larger variety of block copolymers.^[8] This is done by attaching functional groups which start the polymerization of the next polymer block (macroinitiators). Figure 6 shows the schematic structure of a block copolymer obtained by sequential living polymerization. The chain ends α and ω may be functional groups either for molecular binding or for the fixation of superlattices.

There are a large number of published strategies for preparing block copolymers by living anionic polymerization.^[9] Recent years have seen the development of new methods for living cationic^[10] and living radical polymer-

ization^[11] (for example, RAFT technique^[12–15]). New monomers have become accessible for controlled polymerization, which has given rise to the preparation of new classes of amphiphilic or functional polymers. The lower reactivity of the living chain ends enables polymerization to be accomplished with less technical effort (inert gas, high vacuum, rigorous exclusion of air and humidity). Therefore, these polymerization techniques are of considerable interest from a technical point of view. The preparation of block copolymers by means of controlled radical polymerization in aqueous emulsions is currently being investigated. Some block copolymers such as the well-known Pluronic (BASF Wyandotte) and Kraton (Shell) block copolymers, which serve as emulsifiers or as thermoplastic elastomers, are already being prepared on an industrial scale. Table 2 gives a survey of common living polymerization methods together with corresponding monomers.

Table 2. Common living polymerization techniques.

Reactive group	Polymerization technique	Monomers
anion	anionic polymerization ^[a]	styrenes, vinylpyridines, methacrylates, acrylates, butadiene, isoprene, <i>N</i> -carboxyanhydrides (amino acids)
	ring opening ^[b]	epoxides, siloxanes
	GTP ^[c]	methacrylates, acrylates
	ROMP ^[d]	norbornenes
cation	cationic polymerization	vinyl ether, isobutylene
radical	ring opening	oxazoline
	nitroxide polymerization	styrene
	organometals	acrylates
	ATRP ^[e]	styrenes, methacrylates, acrylates, acrylonitriles
	RAFT ^[f]	methacrylates, styrene, acrylates

[a] Industrial products: kraton, solprene. [b] Industrial product: pluronics. [c] Group transfer polymerization. [d] Ring-opening metathesis polymerization. [e] Atom transfer radical polymerization. [f] Reversible addition–fragmentation chain transfer polymerization.

Living polymerization techniques have made it possible to prepare polymers with exact predetermined degrees of polymerization and low polydispersities. The degree of polymerization N of the polymer blocks depends on the molar ratio of initiator I to monomer A and B in the reaction medium: $N_A = [A]/[I]$ and $N_B = [B]/[I]$. The polydispersities are mostly in the range $M_w/M_n < 1.1$, which corresponds to a relative standard deviation in the degree of polymerization of less than 30%.

3.1.2. Polymer-Analogue Reactions

Block copolymers can be further modified by subsequent chemical reaction. The two most important demands on a polymer-analogue reaction are to maintain the block copolymer architecture and to achieve a selective reaction, which should be as complete as possible. To reach the first goal, the reaction conditions must be such that the chains will neither be degraded nor cross-linked. To reach the second goal, reactive and selective reagents are necessary to allow the reaction to be determined by their molar ratio. This is

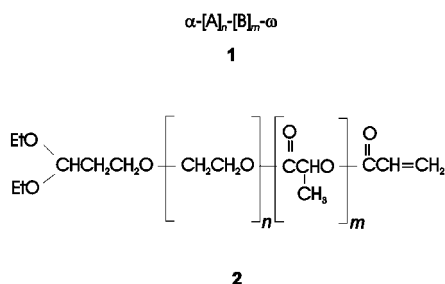


Figure 6. Schematic structure (**1**) and example (**2**) of a functionalized AB block copolymer. **2** is a biocompatible poly(ethylene oxide-*b*-*D,L*-lactide) with an acetal (α) and a methacryloyl end group (ω). The aldehyde group obtained after hydrolysis at the α position is used for the binding of proteins. ω is a polymerizable group for the covalent fixation of superlattices.

important because polymers are often hard to purify after such reactions. A number of polymer-analogue reactions have so far been carried out with block copolymers. These comprise hydrogenation,^[16–19] epoxidation^[20] with subsequent ring opening by nucleophiles^[20] and acid chlorides,^[20] hydroboration/oxidation^[21–24] with subsequent esterification of the OH group,^[21, 22] quaternization,^[25] hydrolysis of *tert*-butylmethacrylates,^[26] sulfonation,^[27, 28] fluorocarbene addition,^[29] and the reaction of olefinic double bonds with *N*-chlorosulfonyl isocyanate for the preparation of blood-compatible heparin analogues.^[30] By means of polymer-analogue reactions the polymer blocks are transformed into blocks of desired solubility, flexibility, and chemical functionality. The solubility of polymer blocks may extend over a range from very polar up to very nonpolar solvents (see Table 3).

3.1.3. Heterophase Polymerization

The outstanding feature of living or controlled polymerizations is their ability to provide more complex polymer architectures. By controlling growth kinetics it has become possible to obtain well-defined polymer structures by means of heterophase polymerization. The mostly spherical particles with diameters from 10 nm to 10 μ m are polymerized in microemulsions,^[31, 32] miniemulsions,^[33, 34] or conventional macroemulsions.^[35] A variety of latex particles made of polystyrene, polyvinyl chloride, polybutadiene, or melamine formaldehyde resins can be produced with very narrow particle size distribution ($\sigma < 10\%$). In the presence of repulsive/attractive force pairs these polymer particles can form superstructures which are important, for example, for the production of photonic crystals or for paint-film formation. Hydrolysis and polycondensation of inorganic silica esters enable monodisperse spherical silica particles (Stöber silica) to be prepared.^[36, 37]

3.2. Structures of Self-Organization

In the following section the self-organization of block copolymers will be described with the help of some examples. They are divided into dilute solutions (micelles, cylindrical micelles, vesicles), lyotropic phases of higher concentration, and bulk phases, each of them being well-suited for the preparation of interesting materials.

3.2.1. Micelles

Surfactants as well as block copolymers form micelles^[38–43] in dilute solutions. As a consequence of the chemical structure of the blocks, block copolymers form micelles not only in polar solutions, such as water, but also in very nonpolar media, such as fluorinated hydrocarbons or supercritical CO₂ (see Table 3). The well-defined micelles have a core consisting of the insoluble A blocks and a shell or corona of the soluble B blocks (Figure 7).

Micelle formation is a simple and well-known example of the self-assembly of polymers. The block copolymers self-assemble to a micelle with defined size and shape. The size of

the micelle depends on the length of the polymer blocks. Figure 8 shows the systematic correlation between the aggregation number Z (the number of block copolymers in a micelle) and the degree of polymerization of the insoluble block, N_A .^[44] The experimental results can be described by a scaling law (1),

$$Z = Z_0 N_A^\alpha N_B^{-\beta} \quad (1)$$

where $\alpha = 2$ and $\beta = 0.8$. Z_0 depends mainly on the enthalpy of mixing between the insoluble polymer block A and the solvent. Scaling laws with fractional exponents such as 0.8 can often be found in polymer systems. Equation (1) describes the formation of micelles for diblock,^[44, 45] triblock,^[45] graft,^[46] and heteroarm star copolymers,^[47, 48] as well as for low molecular cationic, anionic, and non-ionic surfactants, that is over a range of three orders of magnitude in block length N . This proves the universality of such self-assembly mechanisms. The value of Z_0 is tabulated for many block copolymers, and for many systems $Z_0 \approx 1$, which allows the aggregation numbers to be estimated from the degrees of polymerization of the blocks. Thus the aggregation number and the size of the micelles can directly be set through the degrees of polymerization of the blocks. This possibility is of relevance to the preparation of nanocolloids, of porous ceramics, and to drug-delivery systems.

The compartmentization of micelles into a core/shell structure can be well observed in the electron micrograph in Figure 9a.^[49] The micelles have a total diameter of 30 nm, with the core diameter being 10 nm.

In some cases the block lengths can also affect the shape of the micelles. Block copolymers with large soluble B blocks, that is, with small curvature radii R (Figure 4) form spherical micelles preferably, whereas cylindrical micelles or vesicles result from smaller soluble blocks, that is, with greater curvature radii. Cylindrical micelles, for example, of poly(butadiene-*b*-ethylenoxide) (PB-PEO; Figure 9b) may have lengths of several micrometers.^[50] Block copolymer vesicles were observed with diameters from 100 nm up to several micrometers. Polymer vesicles (polymersomes) are mechanically and thermodynamically much more stable^[51, 52] than the well investigated lipid vesicles, and are well suited for the encapsulation and the release of substances. Figure 9c shows vesicles of poly(2-vinylpyridine-*b*-ethylene oxide) (P2VP-PEO) with diameters of more than 10 μ m (giant vesicles) into which, for example, fluorescent dyes can be encapsulated.^[53]

3.2.2. Lyotropic Phases

Higher concentrations of the block copolymers induce lyotropic liquid crystalline phases. Their range of stability can strongly depend on temperature. In aqueous solutions poly(ethylene oxide) (PEO) is usually the soluble block. A temperature increase reduces the solubility of the PEO block, which can result in phase transitions into disordered phases. Most of the current knowledge on lyotropic phase behavior of block copolymers was obtained from studies of poly(ethylene oxide-*b*-propylene oxide-*b*-ethylene oxide) (PEO-PPO-PEO;

Table 3. Solubilities and functionalities of important polymer blocks, arranged according to polarity.

S block	Structure	Remarks
poly(styrene sulfonic acid) (PSS)		strong polyelectrolyte, very hydrophilic (hygroscopic); also Na, K salts; ion exchanger
poly(<i>N</i> -alkylvinylpyridinium halogenide) (PQ2VP, PQ4VP)		strong polyelectrolyte, very hydrophilic (hygroscopic); R = H, Me, Et, Bz; X = Br, I
poly((meth)acrylic acid) (PMAc, PAAc)		polyelectrolyte, hydrophilic; R = H, Me; also Na salts; ionic bond, biomineralization
poly(amino acids) (PAs)		R = (CH2)4NH2 (lysine); R = CH2COOH (aspartic acid), CH2CH2COOH (glutamic acid); drug delivery, biocompatible, biodegradable, biomineralization
poly(<i>N</i> -vinylpyrrolidone) (PVP)		hydrophilic
poly(hydroxyethyl methacrylate) (PHEMA)		hydrophilic; R = OH, NMe2
poly(vinyl ether) (PVEE)		hydrophilic; R = CH2CH2OH, (CH2CH2O)3CH3,
poly(ethylene oxide), poly(propylene oxide) (PEO, PPO)		amphiphilic; R = H, Me; PEO hydrophilic at $T < 80^\circ\text{C}$; PPO hydrophilic at $T < 20^\circ\text{C}$; biocompatible
poly(vinyl methyl ether) (PVME)		amphiphilic; hydrophilic at $T < 70^\circ\text{C}$
poly(ethyleneimine) (PEI)		soluble in hot water (branched also soluble in cold water), synthesis by saponification of poly(2-ethyl-2-oxazoline), papermaking production, gene transfection
poly(4-vinylpyridine), poly(2-vinylpyridine) (P4VP, P2VP)		polar, hydrophobic, ligand, acid–base reactions
polyglycolide, polylactide (PLac, PGly)		R = H (PGly), R = CH3 (PLac); hydrophobic, biocompatible, biodegradable
poly(methyl)acrylate (PMMA)		hydrophobic; R1 = H, Me; R2 = Me, <i>n</i> Bu
poly(vinyl butyl ether) (PVBE)		hydrophobic; R = <i>i</i> Bu
polystyrene (PS)		hydrophobic; R = H, <i>t</i> Bu, CH(SiMe3)2
poly(cyclopentadienylmethylnorbornene) (PCp)		hydrophobic; coordination of transition metals through metallocene complexes
polyethylenpropylene, poly(ethylethylene), poly(isobutylene) (PEP, PEE, PIB)		hydrophobic; R = H, Me
polysiloxane (PDMS)		very hydrophobic (silicone oil); R = Me (biocompatible), Et, Ph; gas separation, low-energy surfaces
partially fluorinated polymers (PF)		very hydrophobic; soluble in freon, CO2; R = C4F9, C8F17; gas separation, low-energy surfaces, emulsion polymerization in CO2

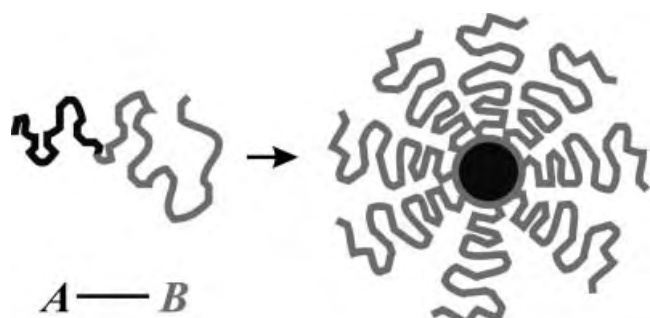


Figure 7. Formation of a micelle (aggregation number $Z=8$) of AB block copolymers as the simplest form of self-organization.

pluronics).^[54] The phase diagrams of block copolymers with shorter chains, in particular, resemble those of low molecular surfactants.

Figure 10 shows electron micrographs of lyotropic block copolymer phases of poly(butadiene-*b*-ethylene oxide) (PB-PEO) in water. The dark regions are the hydrophobic PB domains. There are cubic phases of spherical micelles on a *bcc* lattice, hexagonally arranged cylindrical micelles, and lamellar phases. The periodic length is between 30 and 100 nm and can be controlled by the water content. Homogeneously oriented domains have a dimension of up to several micrometers. Lyotropic phases can be applied to the preparation of porous materials (Section 4.4) while cubic micellar phases are also used in gel electrophoresis to separate proteins and oligonucleotides (Section 5.2). For optimization purposes it is possible to control the morphology and the periodic length through block lengths and polymer concentration.

3.2.3. Bulk Phases

Block copolymers in a micro-phase-separated state are also present in bulk. A variety of copolymer morphologies such as lamellae (LAM), hexagonally ordered cylinders (HEX), arrays of spherical microdomains (BCC, FCC), modulated (MLAM) and perforated layers (PLAM), ordered bicontinuous structures such as the gyroid, as well as the related inverse structures have been documented. The morphology mainly depends on the relative block length. If, for example, both blocks are of identical length, lamellar structures are formed. The stability ranges of the different structures can be represented in a phase diagram as shown in Figure 11 for the system poly(styrene-*b*-isoprene) (PS-PI).^[55, 56] The experimentally determined phase diagram is equivalent to the theoretically calculated diagram

(Figure 5). This proves the efficiency of theoretical approaches.

The periodic length scale of the superlattice can be adjusted over the whole mesoscopic range (from a few up to several hundred nanometers) by varying the degree of polymerization. Figure 12 shows with the example of PB-PEO how the long period d is connected with the degree of polymer-

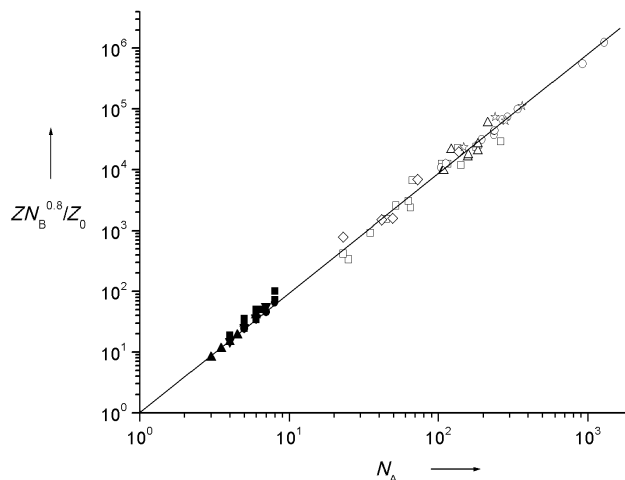


Figure 8. Aggregation numbers Z as a function of the degree of polymerization N_A of the insoluble block. $\circ, \square$: diblock copolymers (PS-P4VP, PS-PMAC), $\triangle$: triblock copolymers (PMAC-PS-PMAC), ∇ : graft copolymers (PSMA-g-PEO), $\star$: heteroarm star polymers (PS-P2VP), $\diamond$: heteroarm star polymers (PS-PAAC), $\bullet$: nonionic surfactants ($C_{12}E_8$), $\blacksquare$: cationic surfactants (RNM₃Br), $\blacktriangle$, $\blacktriangledown$: anionic surfactants (ROSO₃Na, RSO₃Na). (From ref. [44].)

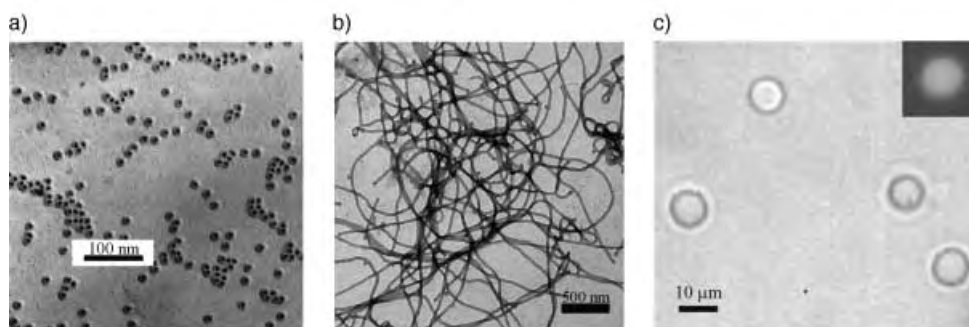


Figure 9. Electron micrographs (a, b) and optical micrographs (c) of the three most frequent forms of self-organization of block copolymers: a) spherical micelles (PS-PI/DMF),^[49] b) cylindrical micelles (PB-PEO/water),^[50] and c) vesicles (P2VP-PEO/water).^[53] Figure c shows top right a single vesicle in which the solution of a fluorescent dye was encapsulated.

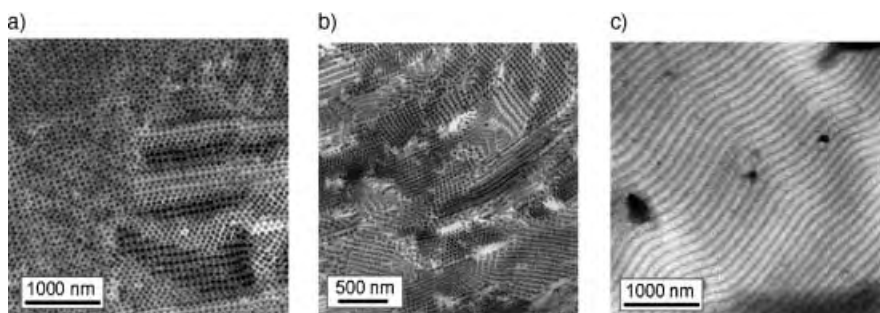


Figure 10. Electron micrographs of a cubic (a), hexagonal (b), and lamellar (c) superlattice of block copolymers in lyotropic liquid crystalline phases. The structure of the lyotropic phases was fixed by γ irradiation.^[50, 95]

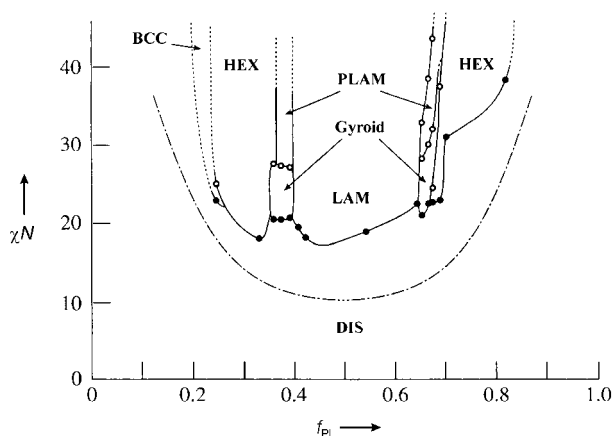


Figure 11. Experimentally determined phase diagram of PS-PI.^[55, 56] The individual superlattices can be specifically prepared by adjusting the volume ratio f_{PI} of the block copolymers, the total degree of polymerization N , and the temperature ($\chi \sim 1/T$). The structures of the individual phases are depicted in Figure 13.

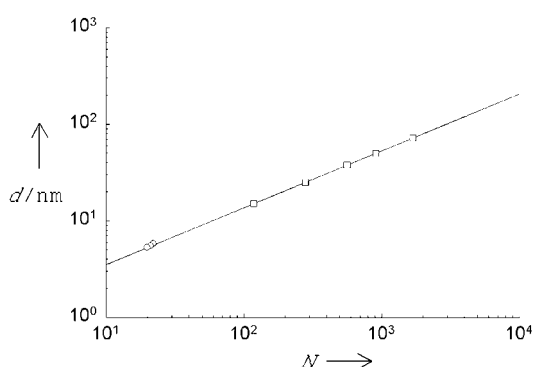


Figure 12. Long period d as a function of the degree of polymerization N of PB-PEO ($\square$) and nonionic surfactants ($\circ$).^[50] The periodic length of the nanostructure can be specifically adjusted over the whole mesoscopic range (1–100 nm) by the degree of polymerization.

ization N . The data points at the lower end of the length scale result from short-chain non-ionic surfactants. This shows the universal behavior of surfactants and amphiphilic block copolymers. In accordance with theoretical predictions, the behavior can be described by a scaling law $d = d_0 N^{2/3}$ ($d_0 = 0.9$ nm) over three orders of magnitude of N . This allows a superlattice of tailor-made size to be chosen from the degree of polymerization of the macromolecule.

The broad variety of self-organizing structures of surfactants and block copolymers is shown in Figure 13. Particulate structures such as spherical and cylindrical micelles as well as vesicles form in dilute solution. Spherical micelles with cubic packing (FCC, BCC), hexagonally packed cylindrical micelles (HEX), and lamellar phases (LAM) form in the solid state, in lyotropic phases, as well as in ternary systems. Besides there are modulated and perforated layer phases as well as cubic

bicontinuous structures such as the gyroid.^[57] By using the phase diagrams one can specifically adjust the morphology of these structures through the choice of block lengths and polymer concentration. Thus, it is possible to prepare tailor-made nanostructured materials.

3.3. Structural Hierarchies

A single self-organization step is often not sufficient to realize functional systems. We are taught from natural processes that several hierarchies of self-organization are often needed. For example, collagen, a connective tissue protein, consists of helices which form a triple helix. It is this structure that results in the special mechanical properties of collagen. As depicted in Figure 14, several hierarchy levels can also be distinguished for block copolymers, their characteristic lengths ranging from 1 nm up to 1 μ m.

The monomers defining the chemical functionality are on the smallest length scale. Several polymerization processes lead to the formation of block copolymers. Their block lengths and block length ratios define a local length scale and a local symmetry. The long-range repulsion and the short-range attraction result in microphase separation, for example, the formation of a micelle. This is the stage in which microcompartments and interfaces form with typical length scales between 10–100 nm. The volume fraction of the microphases and the local geometry of the interface result in different superlattices forming, with the degree of order and the orientation being determined by application of macroscopic fields.

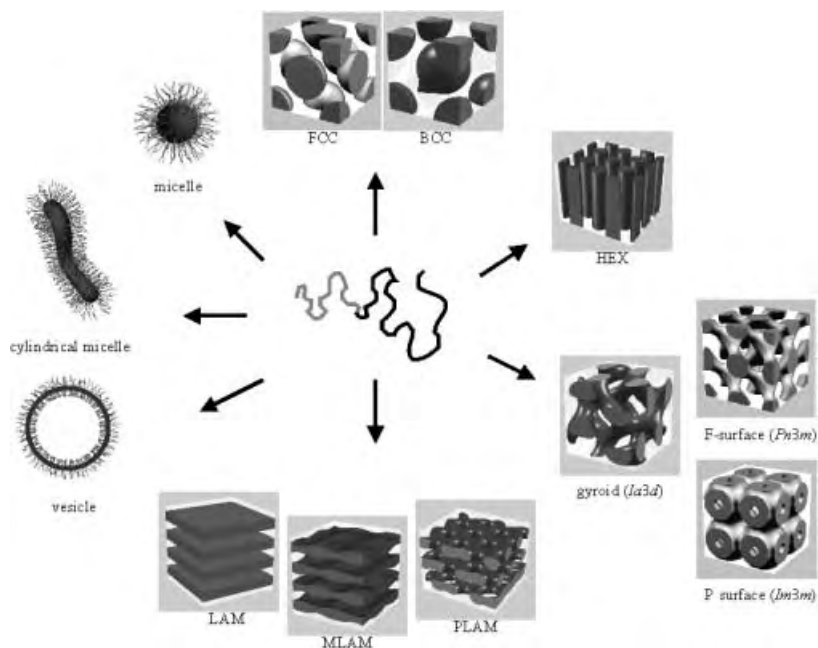


Figure 13. Self-organization structures of block copolymers and surfactants: spherical micelles, cylindrical micelles, vesicles, *fcc*- and *bcc*-packed spheres (FCC, BCC), hexagonally packed cylinders (HEX), various minimal surfaces (gyroid, F surface, P surface), simple lamellae (LAM), as well as modulated and perforated lamellae (MLAM, PLAM).

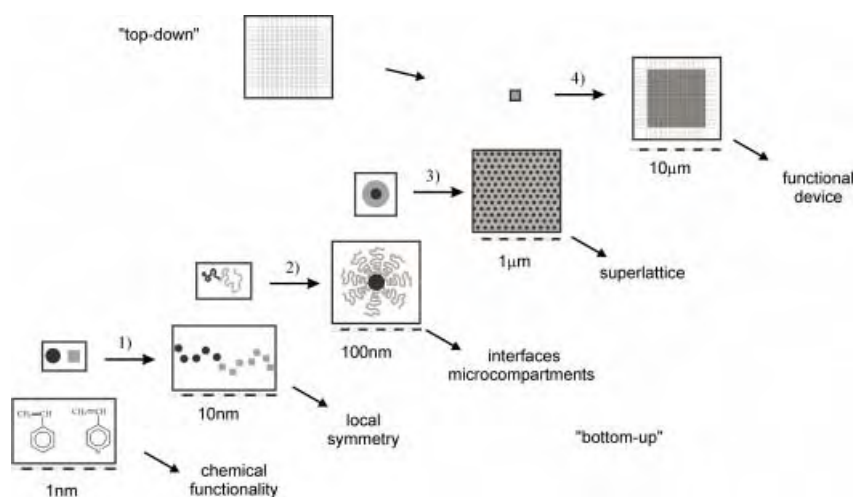


Figure 14. Various structure hierarchies in block copolymer systems. More complex functional systems can be realized by combining bottom-up and top-down strategies.

One advantage of using block copolymers is the high degree of structure control that can be achieved at every stage of the hierarchy:

- 1) Living polymerization is successfully used to specifically prepare block lengths N_A and N_B (Section 3.1).
- 2) The aggregation number and thus the size of the micelle (Figure 8) or the lamellar long period (Figure 12) are directly controlled by the block lengths.
- 3) Depending on the volume fraction of the block copolymer, there is formation of well-defined superlattices in lyotropic phases or in the solid phase, the stability range of which has been documented in phase diagrams (Figure 11).
- 4) External mechanical or electric fields can result in a macroscopic orientation of the superlattices. By this means it is possible to specifically prepare structured materials on a scale of 1 nm to 1 μm .

The stepwise synthesis of ordered structures with the help of self-organization processes is called bottom-up strategy. In contrast to these there are top-down strategies which prepare nanostructures using, for example, lithographic techniques. These methods permit the synthesis of preset addressable structures with a high degree of structure control. As a result of the strong UV absorption of the polymer masks there is a natural limit at about 100 nm for lithographic methods which does not allow the structural elements to be down-sized deep into the submicrometer range. Recently, techniques have been developed which fall below this limit by using scanning microscopy methods.^[58, 59] To get more complex functional systems, bottom-up and top-down strategies can be integrated (see Figure 14). The superlattice is generated in a lithographically produced structure. This helps to avoid the considerable number of defects which often occur in self-organized systems on length scales above 100 nm.

The combination of different principles of self-organization (see Table 1) enables more complicated structural hierarchies to be synthesized. Block copolymers can, for example, be linked to low molecular weight liquid crystals through covalent bonds, ionic interactions, or hydrogen bonds. Thus, the binding of surfactants to poly(styrene-*b*-4-vinylpyridine) (PS-*P*4VP) leads to superlattices as shown in Figure 15a.

Block copolymer cylinders consist of lamellar surfactants.^[60] The lamellar surfactants have a period length of 3 nm while the block copolymer cylinders have a diameter of 30 nm. Extending binary AB systems to ternary ABC systems can result in the formation of complicated superlattices. Highly complex structures such as the “knitting pattern” in Figure 15b found by Stadler and co-workers, form in the presence of ABC triblock copolymers.^[61]

3.4. Compartmentalization

The building of compartments is an important organizational principle in nature. Many metabolic processes become effective only because of the existence of

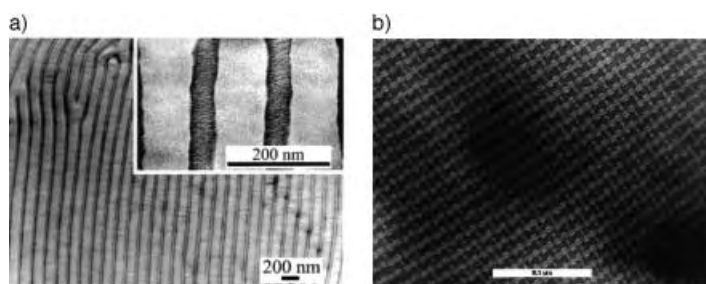


Figure 15. Complex and hierarchic superlattices of AB block copolymer/surfactant systems (a)^[60] and ABC triblock copolymers (b, “knitting pattern”).^[61]

compartments. For example, energy-liberating processes for the production of ATP, such as the oxidation of fatty acids, the citrate cycle, and phosphorylation, take place in special compartments (mitochondria), whereas processes such as fatty acid synthesis and glycolysis are located in the surrounding cytosol. The microphase separation of block copolymers or surfactants can be regarded as a kind of formation of compartments.

In processes of self-organization as well as in the building up of compartments it is possible to distinguish between disperse and continuous compartments or microdomains. A further domain in polymer systems is that of the micelle shells which can be functionalized. These domains are schematically shown in Figure 16.

The micelle cores are appropriate for the solubilization and the storage of substances. The shells are provided with receptors facilitating a specific transport to, for example, tumor cells to deliver pharmaceutically active agents. Low molecular weight as well as high molecular weight substances such as polypeptides and polynucleotides can be stored and transported in different domains. This is of special importance in gene and drug delivery.

The continuous matrix is used mostly because of its permeability and its mechanical stability. The permeability together with the partition equilibrium with the hydrophobic domain are the principles of separation when using lyotropic

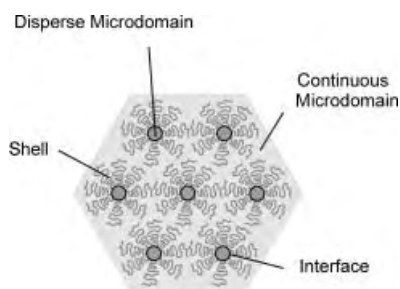


Figure 16. Different compartments in polymer systems which can be used for various functions such as transport, storage, addressing, and chemical reaction.

phases in chromatography. The mechanical stability plays an important role with respect to the properties of thermoplastic elastomers and high-impact materials.

Table 4 summarizes previous work on the utilization of polymer compartments such as micelle cores, micelle shells, and matrices. The materials used cover a wide range: from organic drugs and dyes to inorganic materials up to biopolymers and plastics. This wide variety is also evident in the different applications. In order to purposefully place functional groups in the outer shell, the chain end of the soluble polymer block should be chemically activated (Figure 6). This can be achieved through special initiating and terminating reactions during living polymerization.

3.5. Solubilization and Adhesion

For utilization purposes, it is necessary to “fill” the compartment, that is, to solubilize particular substances. This

is mainly done by using secondary valence forces. These comprise the classical mechanisms of physi- and chemisorption:

- cohesion energy density, solubility, for example, toluene/polybutadiene;
- acid–base interaction, for example, $\text{HAuCl}_4/\text{poly}(\text{vinylpyridine})$, $\text{ZnO}/\text{polymethacrylic acid}$;
- complex formation, for example, Au/thiols , $\text{Pd}/\text{polybutadiene}$;
- hydrogen bridges, for example, $\text{SiOH}/\text{polyethylene oxide}$.

These interactions can be used to stabilize the interfaces between polymers and inorganic materials. The adhesion of both materials acts as the “glue” which holds the supramolecular structures together.

If solubilization takes place mainly through differences in the cohesion energy density, this can be explained by a simple thermodynamic description from which one can derive a scaling law $\phi_{\text{max}} \sim \chi^{-b}$ for the solubilization capacity ϕ_{max} . ϕ_{max} is the maximum quantity of solubilized substance per block copolymer, χ the Flory–Huggins interaction parameter, and b a positive empiric constant. Cohesion energy densities and their relative χ values have been tabulated in standard works. Nagarajan et al. found this relation when they investigated the solubilization of aliphatic and aromatic hydrocarbons,^[62] alcohols, ethylene esters, ketones, and aldehydes, all of which are typical components of food flavoring.^[63]

For many applications not only does the solubilization capacity play a decisive role, but also the selectivity does, that is, the accumulation of particular substances from mixtures. The lower entropy of mixing in polymers results in a higher selectivity than can be expected for low molecular weight surfactant systems. Investigations focused on the selectivity in

Table 4. Use of polymeric compartments.

Materials, substance	Solubilization	Storage	Transport	Release	Chemical reaction	Application, function
micelle cores						
dyes	×	×				de-inking
odorous substances		×		×		perfumes
drugs	×	×		×		drug delivery chemotherapy
proteins	×	×	×	×		drug targeting
DNA	×	×	×	×		gene therapy
inorganic precursors	×				×	nanoparticle synthesis, biomineralization
noble metals	×	×			×	catalysis
semiconductors	×	×				electroluminescence, UV protection, cell marking
enzymes	×	×			×	mitochondrion
elastomer						high-impact and tear-resistant plastics
micelle shells						
polymer block						
PEO			×			solubility
heparin			×			stealth particles
enzymes					×	anticoagulant
RGD sequence			×			catalyst support
IgG			×			detection
polyelectrolyte						endogenic vectors
dye						ion exchange
ligand		×				labeling
matrix						heavy metal binding
inorganic sols						
proteins		×			×	mesoporous ceramics
polynucleotides		×				gel electrophoresis
polymers	×	×	×			gel electrophoresis
gases		×				gel permeation chromatography
elastomer						gas separation
						rubber, hydrogel

the solubilization of orange oil components,^[64] polycyclic aromatic hydrocarbons,^[65] benzene,^[66] xylene,^[67, 68] and fluorescent probes.^[69] All these experiments show that very large solubilization capacities and high selectivities can be achieved through the use of block copolymer micelles. The fourfold difference between the solubilization of benzene and hexane in a low molecular weight surfactant (SDS) is much less compared to the 20- to 40-fold difference in block copolymers.^[62]

Block copolymers are also able to solubilize or adhere to inorganic materials. This feature is of special relevance for the controlled synthesis of inorganic colloids and the controlled assembly of hybrid materials. The incorporation of inorganic materials into polymeric domains can be achieved through ligands. These ligands are also able to stabilize the contact surface between metals and inorganic materials. The ligands should be chosen based on Pearson's hard and soft acid and base (HSAB) principle. In the HSAB sense, most metals are soft and acidic and are therefore well-stabilized by soft bases, such as thiols and phosphanes, known as "capping agents" from the synthesis of small metal clusters. Many semiconductors and metal oxides are fairly soft and most of them are bases, therefore, fairly soft acidic ligands such as alcohols, phosphates, and carboxylates provide good stabilization effects.^[70] The stabilization of inorganic polyacids, which are of relevance as intermediates in sol/gel processes, can proceed through formation of hydrogen bridges (for example, with polyethylene oxide). The solubilization of polymers^[71, 72] and biopolymers^[73] is partly achieved through Coulombic interactions.

The specific interface in materials with nanodomains is very large, therefore, it is essential to stabilize it sufficiently in order to achieve stable hybrid systems. The interface per volume is given by $A_v = D\phi/R$ where D is the dimensionality of the domains ($D=3$ for spheres, $D=2$ for cylinders, $D=1$ for lamellae), ϕ is the volume fraction of the nanodomains, and R is the radius (or half diameter) of the domain. Thus, a material with spherical domains of 1 nm diameter at a volume fraction of 50% ($\phi=0.5$) has an interface of $3000 \text{ m}^2 \text{ cm}^{-3}$ interface(!), which is nearly the size of a football field that has to be stabilized. The following example of the adhesion between natural rubber and brass-plated steel for the steel cord tyre application is an illustration of such a concept. There is only poor adhesion between natural rubber and steel because of their difference in hardness (in the HSAB sense). Interestingly, brass-plated steel was found to bind much more effectively to natural rubber. Sulfur (the cross-linking or vulcanizing agent) actually also functions as a chemical adhesive between natural rubber and brass to form the $\text{Cu}_2\text{S}/\text{ZnS}$ interphases.^[74] Alkyl sulfides are soft bases which preferably bind to soft acids such as Cu. The binding of rubber to metallic cord fibers in this manner is responsible for the performance of the present generation of tyres. This is a good example of the challenges one has to overcome when constructing stable nanohybrid materials.

Interfacial energies are also fundamentally related to properties of material in the area of bioadhesion. Materials with an interfacial tension γ between 20 and 30 N m^{-1} bind very weakly to the surface of cell tissue. This has to be taken into account when adapting the surface of implants in a way to

avoid the occurrence of blood clots and thrombosis. Polymers such as polydimethylsiloxane ($\gamma = 22 \text{ N m}^{-2}$) and polyisobutylene ($\gamma = 30 \text{ N m}^{-2}$) are well suited for surface modification of materials.

3.6. Structure Fixation

It is often necessary to add substance, to initiate chemical reactions, and to change temperature and concentration for self-organized structures to be used. These changes may result in a destabilization of the structure. Chemical and physical cross-linking can, however, stabilize the superlattices. It is possible to cross-link the disperse phase (micelle core, micelle shell), the continuous phase (matrix, matrix + shell), or both phases (Figure 17).

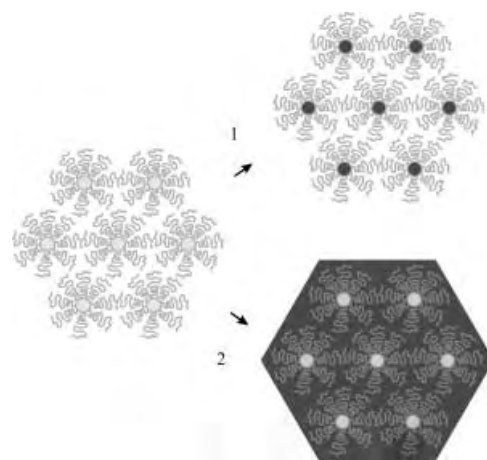


Figure 17. Structure stabilization in polymer systems by fixation of the micelle cores (1) or the micelle shells (2).

The increase of the molecular weight resulting from cross-linking is in many cases sufficient to initiate phase transitions into other superlattices. This represents a problem mainly with superlattices of low molecular weight surfactants. Only in very few cases was it possible to stabilize lyotropic phases by using cross-linkable low molecular weight surfactants.^[75, 76] Polymer superlattices are thermodynamically more stable and are, thus, easier to stabilize. An overview of the most common cross-linking reactions is given in Table 5.^[50, 77–95]

A simple fixation of lyotropic polymer phases is achieved by means of γ irradiation.^[50, 95] Cross-linking by γ irradiation is possible when the rate of depolymerization is lower than that of cross-linking. If this condition, which is prerequisite for both blocks in the case of block copolymers, is met this method is a very efficient one for combining high cross-linking efficiency with high penetration depth and minimum change of the thermodynamic state. It is, for example, well suited for fixation of the superlattices of lyotropic phases so that the obtained gels can be swollen or dried whilst maintaining their structure. The electron microscopy investigation of the lyotropic phases in Figure 10 were obtained from thin layers of the dried gels obtained by this method.

After fixation, well-defined stable superlattices are obtained which can undergo further chemical change and

Table 5. Fixation of supramolecular structures.

Cross-linking	Reaction	Example
photochemical	[2+2] cycloaddition	anthracene, cinnamic acid, diacetylene ^[77–80]
chemical	radical recombination	photoinitiator, e.g. irgacure
	polycondensation	epoxy resin, ^[81, 82] polyester ^[87]
	sol/gel process	silicic acid
	quaternization	1,4-dibromobutane, <i>p</i> -dibromoxylylene ^[83–85]
thermal	radical recombination	redox initiator, e.g. Ce ⁴⁺ ^[86, 87] fragmentation, e.g. AIBN, dibenzoyl peroxide ^[88–92]
radiochemical		⁶⁰ Co ^[50, 95]
secondary valence bond	H-bonds	cytosine/guanine
	ligands	chelates
	Coulombic	simplex formation ^[93, 94]
physical	supercooling, freezing	cooling below glass transition temperature (“frozen micelles”), fast crystallization

functionalization. The functionalization of molecular surfaces is an important aspect, as is the case with dendrimers and fullerenes. Various structures can be classified according to their curvature radii (Figure 18). Plane surfaces have a curvature radius approaching infinity.

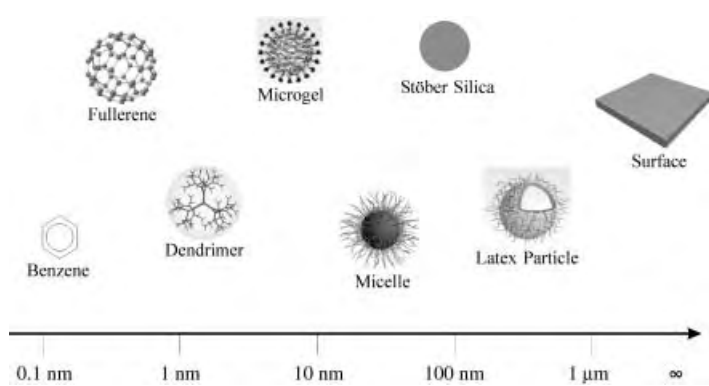


Figure 18. Particles with defined topology and surface ordered according to the curvature radii R of their surfaces. The surfaces can be functionalized through specific chemical reactions.

Whereas many supramolecular systems are synthesized stepwise from smaller molecules (dendrimers, macrocycles), a number of larger molecular systems are formed by self-organization or by specific control of growth kinetics. This applies for fullerenes as well as for micelles or latex particles. It is often much easier to synthesize larger molecular structures by using physicochemical concepts than by a stepwise chemical synthesis. Many procedures taking place on an industrial scale have long made use of such concepts. The “price” to pay for the use of these physicochemical concepts is a certain size distribution of the self-organized structures. However, the relative standard deviation is in many cases only a few percent. Fractionation methods allow this value to be further decreased, so that in some cases only one species, for example, in the case of C₆₀ fullerenes, is obtained.

4. Inorganic Nanohybrid Materials

Nanostructures represent the transition from atom to solid. Their special optical, electronic, magnetic, and chemical properties are the result of size quantization effects as well

as of the high number of surface atoms and the subsequent special surface states. These properties favor nanostructures to be applied in the areas of signal transmission, data and energy storage, as well as catalysis.

An important goal of materials science is the controlled and specific synthesis of well-defined nanostructures comprising nanoparticles as well as nano- and mesoporous materials. It is essential to obtain particles or pores with uniform diameters and shapes and, for the purpose of particular applications, to arrange and embed them in a superstructure.

In order to produce inorganic nanoparticles the materials are either mechanically crushed in a conventional manner or synthesized from precursor compounds by controlling the crystal growth kinetics. For the production of ferrofluids, for example, it is necessary to pulverize magnetite particles to a diameter of < 100 nm in a ball mill for one week! Appropriate ligands have to be added to stabilize the extremely large specific surface. The same applies to controlled growth kinetics. It has become possible to produce nanometer-sized uniform metal or semiconductor particles of some materials.

Nanoparticles can also be synthesized in the microcompartments of self-organized systems. This possibility offers the advantage of restricting the size growth of the particles to a definite diameter and preventing the particles from aggregating into larger sizes. If the microcompartments are arranged on a superlattice this kind of synthesis results in the nanoparticles also becoming integrated into the lattice. This situation gives rise to the formation of nanostructured inorganic/polymer hybrid materials. The extremely large inorganic/polymer interface can be stabilized by binding appropriate ligands to the polymer blocks.

Figure 19 is a schematic diagram of how nanocolloids can be prepared in polymers. The synthesis is similar to that in usual reaction flasks. The starting material is introduced into a compartment of appropriate size by solubilization (1). With adequate sorption provided, the material is distributed into the compartment by simple stirring, impregnation, or swelling. The next step is the chemical conversion to the desired material (2). For this purpose an additional reagent has in some cases to be added, a sufficient permeability being necessary which is directly connected with the solubilization and the diffusivity of the matrix. Both factors are prerequisite for an optimized synthesis. Gaseous reagents are often used for high diffusivities; these can quickly diffuse into the compartment. Alternatively the compartment material itself can be used as a reagent.^[96]

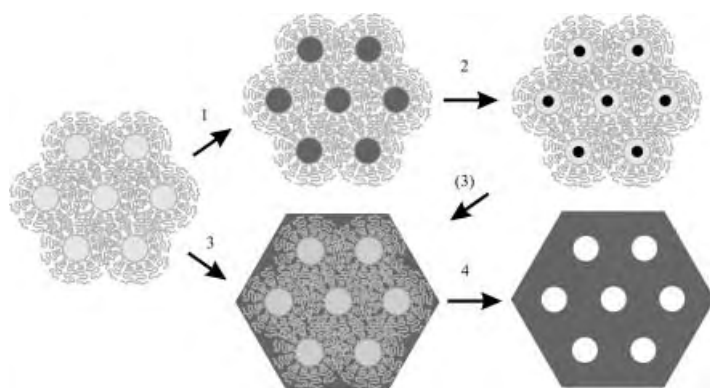


Figure 19. Synthetic scheme for the preparation of nanostructured hybrid materials. Nanoparticles (by steps 1 and 2) and mesoporous structures (by steps 3 and 4) can be synthesized. Steps 1 to 4 lead to pore structures with embedded nanoparticles.

After chemical reaction has taken place, small inorganic primary particles are formed which are homogeneously distributed in the microdomain. Depending on the strength of the ligands, the primary particles can be stabilized at this stage or they can further grow inside the microdomain. The size of the resulting inorganic particles depends on the conditions of nucleation and growth (concentration, size of domain, viscosity of the matrix, stabilization of the interface). Thus, nano-sized single crystals of uniform size can be prepared in the microdomains under appropriate conditions. The particle size can exactly be adjusted through the quantity of inorganic precursor material per microdomain. For many applications, for example, electrooptics, or catalysis, the material can remain in the compartment or in the matrix.

Figure 19 also shows how the continuous domain can be used for the preparation of porous structures. A sol/gel process leads to a continuous inorganic network in the matrix (3). After removing the block copolymer by extraction or calcination, one obtains the porous material. The shape and the diameter of the pores correspond to the hydrophobic microdomains of the polymer phase. Nanocolloids embedded in the pore structure can be obtained by following steps 3 and 4 after 1 and 2.

4.1. Metal Hybrids

Small metal clusters represent the transition from metal atom to solid state. The cluster size decides on the optical, electronic, and chemical properties of the metal. Thus the standard potential of the silver atom (Ag), increases through n -atomic silver clusters (Ag_n) up to solids (Ag_∞) from -1.8 to $+0.8$ V. Collective oscillations of the electrons lead to plasmon resonances which in the case of metal clusters belonging to group Ib (Cu, Ag, Au) cause strong absorptions in the optical range ($400 \text{ nm} < \lambda_{\text{max}} < 600 \text{ nm}$). As the refractive index takes on high values near a strong absorption band, such systems are being investigated for applications in non-linear optics. Most of the atoms of small metal clusters are surface atoms. Special surface states combined with the large specific surface area lead to extraordinary catalytic properties.

To prepare metal clusters in polymer matrices (polymer/metal hybrids), the interface between both materials has to be stabilized sufficiently. According to the HSAB concept, metals are mostly soft acids and it should, therefore, be possible to stabilize them well with soft bases. Thus, polymer blocks functionalized with N, S, or P ligands are applied. Unstable metal complexes with hard bases (chlorides, acetates) serve as precursor materials which, by complexing with the softer ligands, can be solubilized into the polymer compartments. The complexation between the precursor and the ligand must not be too strong otherwise there will be no further reaction to the elementary metal.

Figure 20 shows electron microscopic images of micelles of poly(styrene-*b*-4-vinylpyridine) (PS-P4VP). For the preparation of Au nanocolloids, HAuCl_4 was solubilized as the precursor into the P4VP micelle core. After reaction with a strong reducing agent (LiAlH_4) has taken place, small primary

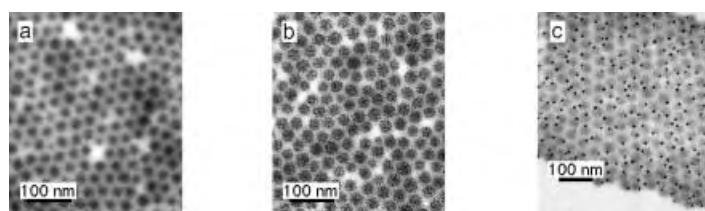


Figure 20. Preparation of gold nanocolloids in micellar block copolymer systems.^[104] a) Micelles loaded with the precursor (HAuCl_4), b) Au nanocolloids after fast reduction, c) Au nanocolloids after slow reduction.

Au particles with a diameter of about 1 nm develop in the micelle core. One single crystal with a diameter of 3 nm arises per micelle core upon slow reduction with Et_3SiH as a reducing agent. The micelle shells prevent further growth to colloidal aggregates.^[104] A number of metal colloids such as Au,^[97–107] Ag,^[97, 98, 106] Pd,^[98, 106, 108–111] Pt,^[98, 107, 108, 110, 112] Cu,^[98] Ni,^[98] Pb,^[98] Rh,^[106, 112] and Co^[113] can be prepared in this way.

Co clusters with a diameter below 20 nm consist of a magnetic single domain (Weiss region). Solutions of such clusters are called magnetic liquids or ferrofluids. They show superparamagnetic behavior. Ferrofluids are being investigated with regard to their suitability as sealing liquids and magnetic inks for printers as well as for medical applications (artificial muscles, tumor diagnostics, and cancer therapy). The clusters, being fixed in a matrix, keep the direction of magnetization and store magnetic information.

The giant magnetoresistance (GMR) in magnetic nanodomains discovered in 1988 represents an example of how fast nanomaterials find acceptance in technical applications. It was possible to develop very sensitive sensors for magnetic fields which were integrated into read/write heads for magnetic storage systems. Meanwhile, these systems have completely replaced the former conventional ones. New magnetic storage systems (MRAMS) with storage densities of 10 GB per chip and access times below 10 ns are being developed based on the GMR effect.

Of special significance are the catalytic properties of small metal clusters. At their surface, such clusters have a large number of atoms with a low coordination number to which substrates bind. Catalytic hydrogenation, hydrosilylation,

hydration, and the Heck reaction are being studied. Moreover, metal clusters are of importance with regard to redox and electron-transfer processes such as the photochemical decomposition of water (fuel cells) and photocatalytic hydrogenation.

The outstanding features of metal clusters prepared in block copolymer micelles^[114] are their high catalytic activity combined with high stability. Such micellar catalyst systems can be recovered after reaction by precipitation or ultrafiltration. In some cases high stability has been observed. Cyclohexadiene, for example, is selectively hydrogenated by Pd colloids only to cyclooctene.^[102]

Special attention has been focused on studies carried out on the Heck reaction. This reaction is of great interest in preparative organic and macromolecular chemistry, for example, in the synthesis of luminescing poly-*p*-phenylenevinyls (PPVs). Figure 21 shows the percentage of reaction for

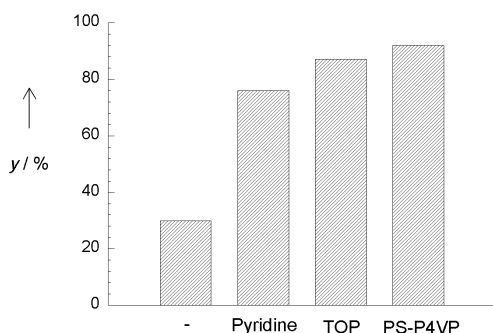


Figure 21. Percentage of reaction y of the Heck reaction with Pd without ligand and for different ligand systems.^[114] The catalyst embedded in the micelles shows the highest reaction at considerably better stabilizing. TOP = tri-*o*-tolylphosphane.

different ligand systems in the coupling of bromacetophenone and styrene to the stilbene product. Without stabilizing ligands the activity remains low, and after some time “palladium black” is observed. This is avoided by using stabilizing ligands. Pd clusters embedded in block copolymer micelles show the highest activities. A proof of the good stabilization are the high turnover numbers (70 000 mol product per mol catalyst) which are clearly higher than those of other systems investigated.

4.2. Semiconductor Hybrids

Reducing the diameter of semiconductor particles to a few nanometers results in a change of their electronic properties. Confinement to the nanometer range is possible in one, two, and three dimensions, that is, in the form of quantum wells, quantum wires, and quantum dots. These quantum structures serve as control and storage elements which can be switched with one single electron (or its spin), which enables very high computing speeds to be achieved.

Reducing semiconductor nanoparticles to the nanometer scale results among other things in:

- 1) an increase of the band gap by several eV (size quantization effect), which leads to a blue shift of the absorption and of the photo- and electroluminescence;

- 2) an increased energy of photogenerated electrons which is utilized, for example, in photovoltaics, and
- 3) an increase in the optical absorption coefficient which is significant for applications related to UV protection.

Normally semiconductor structures are prepared by means of top-down technologies such as photolithography or molecular beam epitaxy. Recently bottom-up methods have been successfully studied. By using self-organization processes and by controlling growth kinetics these methods can be used to prepare quantum dots and nanoparticles in high quality. Monodisperse nanoparticles of CdS, CdSe, CdTe, InP, and InAs, which are able to organize in superlattices, have been prepared. It is furthermore possible to synthesize semiconductor nanoparticles in the superlattices of block copolymers.^[104] Semiconductor clusters of CdS,^[115–117] ZnS,^[116, 118, 119] PbS,^[116, 120] ZnF,^[119] CuS,^[116] CoS,^[116] FeS,^[116] and ZnO^[121] are mostly generated by sulfidic precipitation with H₂S.

Size control is an important goal when preparing semiconductor nanoparticles. This can be achieved by varying the size of the block copolymer domains. In smaller domains we observe smaller semiconductor particles which, as a result of the size quantization effect, have absorption edges or smaller wavelengths. Figure 22 shows this blue shift of the absorption band with decreasing particle size of CdS clusters. A CdS solid has an absorption edge at $\lambda = 480$ nm. Small CdS nanoparticles have an absorption edge shifted below 400 nm. These particles were synthesized in polymethacrylic acid domains of poly(styrene-*b*-methacrylic acid) (PS-PMAC).

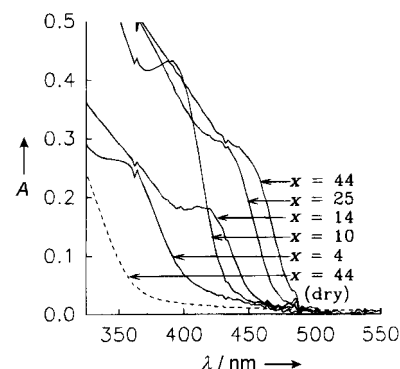
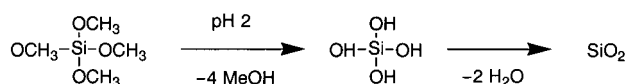


Figure 22. Blue shift of the absorption edge of CdS with decreasing particle size (size quantization effect).^[115] The particle size was adjusted by the degree of polymerization x of the polymethacrylic acid block.

Semiconductor particles with tunable optical properties are well-suited for applications in optoelectronics and communication technology where with higher transfer frequencies and a more efficient use of the optical spectrum larger band widths for data transfer can be achieved. Quantum dots have recently been used as fluorescent labels for biological tagging experiments in diagnostics and for visualizing molecular processes in living cells.^[122, 123] TiO₂ particles with diameters of 10–30 nm have been studied with regard to their application in photovoltaics (Graetzel cells) or as photocatalysts for the photo-oxidation of waste water contaminations.^[124]

4.3. Glasses, Ceramics, and Biominerals

Nanostructured inorganic materials and inorganic/polymer hybrids are known for their good mechanical and thermal properties. They are often harder and less fragile than the same material without inner structuring. Nature provides innumerable examples of inorganic/polymer composites such as bones, teeth, and shells. Such hybrid materials can be prepared by means of controlled crystallization, by sol/gel processes in microcompartments, or by mixing polymers with layer silicates. In sol/gel processes a hydrolysis and subsequent condensation of inorganic precursor materials take place, as a result of which amorphous inorganic materials originate, for example, upon preparing silica by hydrolysis of tetramethylethoxysilicate and subsequent condensation (Scheme 1).



Scheme 1.

When carried out in nanostructured polymer matrices, this reaction leads to mechanically stable silica/polymer hybrid materials. The polymer matrix can be removed by means of calcination and the pure minerals are obtained. Nanometer-sized glass or ceramic particles originate, depending on the topology of the microstructure. Wiesner and co-workers succeeded in preparing spherical, cylindrical, and pellet-shaped silica particles from hybrid materials.^[125]

Mineral/polymer composites are prepared in nature by crystallization in the presence of particular proteins (biomineralization). It has not yet been possible to elucidate the function of these proteins in detail. It is, however, possible to simulate many of these functions with block copolymers.^[126] For this purpose various systems such as CaCO_3 ,^[127–129] $\text{Ca}(\text{HPO}_4)$,^[130] ZnO ,^[131] and BaSO_4 ^[132, 133] have been investigated. The crystallization depends on the binding polymer block, such that CaCO_3 , for example, can crystallize as calcite, vaterite, or aragonite. The formation of spheres, hollow spheres, dumbbells, or fibers was observed depending on the conditions of crystallization.^[126] The way block copolymers operate in the case of controlled biomimetic mineralization is based on their specific adhesion to particular crystal growth surfaces as well as on a steric stabilization of the microcrystals originating.

Polymer nanocomposites are being investigated with regard to their application as substitutes for metals in the motor industry, for the reinforcement of polymer fibers and tyres, as scratch-resistant and inflammable coatings, and as biocompatible materials for prosthetic use.

4.4. Porous Inorganic Structures

Porous materials can be distinguished according to their pore size as microporous ($d < 2$ nm), mesoporous ($2 \leq d < 50$ nm), and macroporous ($d \geq 50$ nm; Figure 23). Zeolites belong to the most important microporous inorganic materi-

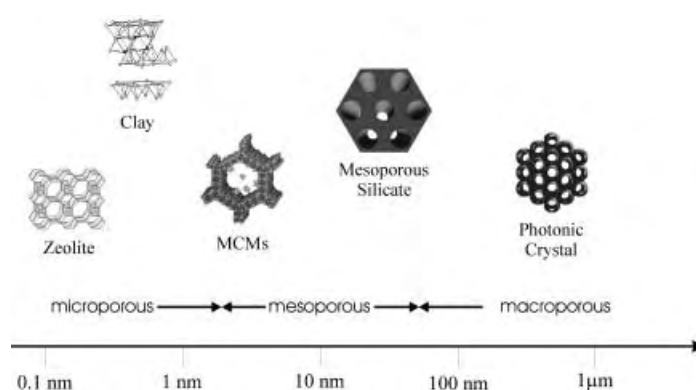


Figure 23. Typical length scales of three-dimensional porous structures.

als. These are crystalline aluminosilicates with a framework structure consisting of cavities and channel systems of defined size and shape. The pore diameter depends on type of zeolite and is between 0.4–1.5 nm. As a consequence of this structure, zeolites have particular properties, such as the ability to exchange ions and to reversibly desorb water. These properties are made use of when employing zeolites as ion exchangers and molecular sieves. Above all zeolites are applied as catalysts, and in the area of petrochemistry alone (ZSM-5, zeolite Y) there is an annual turnover of more than US\$ 30 billion. The catalytic properties of the zeolites result from Brønsted acid centers at the inner surface and from the electrostatic field inside the cavities and the channels.

Mesoporous materials with pore diameters of more than 2 nm were developed by Mobil Co. in 1992 and were called MCM materials. They are amorphous silicates or aluminosilicates with pore sizes between 1.6 and 10 nm. This larger pore size represents a considerable advantage over zeolites because much bigger molecules can be received and made to react.

Similar to some zeolite syntheses, short-chain surfactants are used to synthesize MCMs. In aqueous solutions these surfactants form micellar phases, where the dissolved silicate species is made to condensate. In this way amorphous silicate walls, about 1-nm thick, originate between the micelles. Lyotropic, lamellar, hexagonal, and cubic phases develop, depending on the concentration of the surfactant, which leads to varying silicate structures. Materials with free pore systems are obtained after thermal removal of the surfactant by calcination.

Lyotropic phases of block copolymers are well-suited for the preparation of mesoporous inorganic materials with still bigger pore diameters. Pore diameters and a wall thickness of more than 50 nm lead to mechanically stable monolithic materials. According to the structure of the lyotropic phases, porous cubic, hexagonal, and lamellar structures can be prepared (Figure 24).^[95, 134] By means of the sol/gel process it is possible to prepare mesoporous SiO_2 ,^[135–146] TiO_2 ,^[146, 147] NiO_2 ,^[147] ZrO_2 ,^[147] Al_2O_3 ,^[147] Nb_2O_5 ,^[147] Ta_2O_5 ,^[147] WO_3 ,^[147] HfO_2 ,^[147] SnO_2 ,^[147] as well as mixed oxides such as $\text{SiAlO}_{3.5}$,^[147] SiTiO_4 ,^[147] ZrTiO_4 ,^[147] Al_2TiO_5 ,^[147] and ZrW_2O_8 .^[147] The porous inorganic material is obtained after removing the polymer by calcination. The size and shape of the pores are predetermined by the hydrophobic domains in the lyotropic phase.

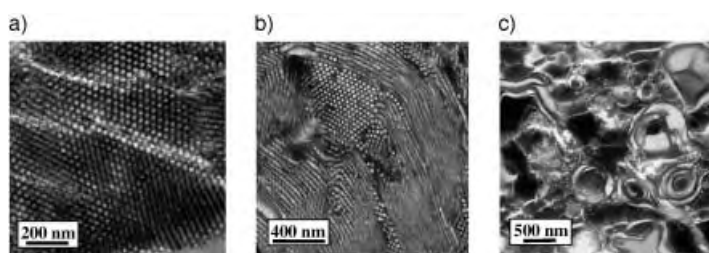


Figure 24. Silicates with a) spherical pores of cubic order, b) hexagonally ordered cylindrical pores, and c) lamellar pores prepared from lyotropic phases of block copolymers.^[95, 134]

Studies are currently being carried out on a large number of applications for mesoporous structures, for example,

- as sorbents for the removal of heavy metals from sewage and of gaseous contaminations from natural gas,
- as hydrogen and methane reservoirs for fuel cells,
- as catalysts and catalyst supports,
- as transparent thermal insulating layers,
- for the storage and controlled delivery of plant nutrients (fertilizers, water).

Intensive investigations are currently being performed on how to vary the chemical composition of the silicates, to coat the surface, to vary the pore size, and to fix catalysts at the surface.^[148]

Macroporous materials with pore diameters of more than 50 nm which can be generated with the aid of polymer latex particles are being investigated with regard to their applicability as photonic crystals. The periodic length of the crystal structure must be in the range of some 100 nm in order to prepare a photonic crystal working in the region of wavelengths of visible light. Monodisperse polymer latices are used which organize spontaneously under high concentrations to form cubic superlattices. An inorganic matrix can be prepared in the interspaces filled with water by means of the sol/gel process. A porous inorganic structure is obtained after removal of the latex particles by calcination (Figure 25).^[149] The shape and size of the pores and the pore distances correspond to those of the latex particles in the self-assembled superlattice. Materials with high dielectric constant (TiO_2 , semiconductors, metals, chalcogenide glasses) are used as the matrix. The size of the photonic band gap can be adjusted by the periodic length and the dielectric constant of the matrix. Superlattices with photonic band gaps are only transparent for particular regions of wavelength and are used for low-loss guiding and switching of optical signals.

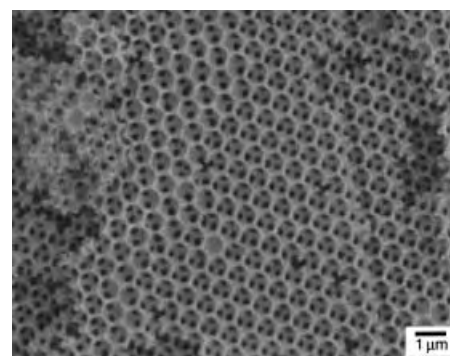


Figure 25. Photonic crystal synthesized from polystyrene latices by a sol/gel procedure.^[149]

The following example shows how the bottom-up and top-down strategies can be combined for the generation of functional structure hierarchies (Section 3.3). Periodic structures (triangles linked by bridges) with a periodic length of $d_1 = 15 \mu\text{m}$ are produced by microcontact printing (Figure 26). The bridges and triangles consist of porous SiO_2 with pore sizes of $d_2 = 500 \text{ nm}$ (achieved by the templating of latex particles) and of $d_3 = 2 \text{ nm}$ (lyotropic block copolymer phase).^[150] Microscopy images of these three structural levels are depicted in Figure 26. Such porous silicate structures have a low refractive index ($n \approx 1.15$) and can be loaded with laser dyes. They are currently being studied as wave guides for lasers in integrated optical systems.^[151]

5. Biomaterials

The organization and functionalization of molecules on several size scales is one of the key properties of biological systems. Many of these functions can be imitated by using self-organized structures, with the material properties of the polymers playing an important role. Only 10 to 20 different polymers are currently used as biomaterials. Most of them were initially not developed for clinical purposes, but were chosen according to trial-and-error procedures. A lot of them cause long-term side effects and complications when used in medical applications. The future generation of polymer biomaterials will be systematically developed and shall offer a broad spectrum of specific applications and functions with the highest possible safety.

There is a wide variety of functional polymers able to adopt functions such as encapsulation, stealth, cell adhesion, and cell

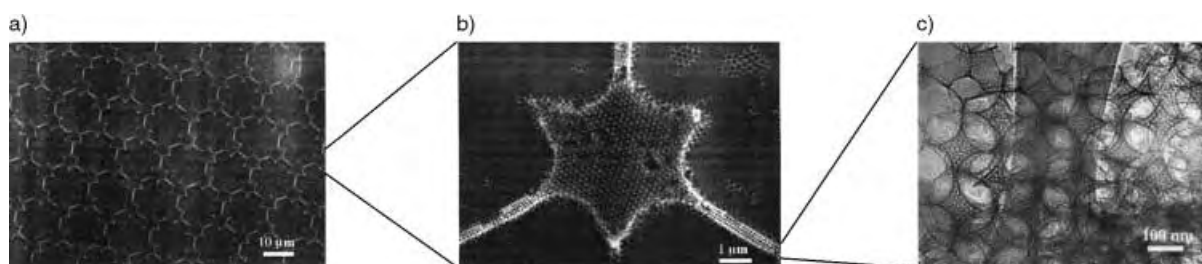


Figure 26. Electron micrographs of a structure hierarchy over three organization levels^[150] prepared with the aid of microcontact printing and self-assembly: a) microcontact sample ($d = 15 \mu\text{m}$), b) macroporous structure ($d = 200 \text{ nm}$), c) mesoporous structure ($d = 2 \text{ nm}$).

recognition as well as different actuator functions (Figure 27, Table 6). Polymers must be biocompatible. This feature is influenced predominantly by the polymer surface. Polymers with hydrophilic surfaces are often well-suited and so are those with an inert surface, that is, which have a surface tension of $\gamma < 30 \text{ N m}^{-1}$ (teflon, polysiloxan, polyisobutylene). Hydrophilic, noninteracting materials cannot be recognized by living systems (stealth systems) and therefore have low cytotoxicity. It is often advantageous to introduce functional groups into the polymer chain in order to bind bioactive molecules such as peptides, oligosaccharides, and antibodies.

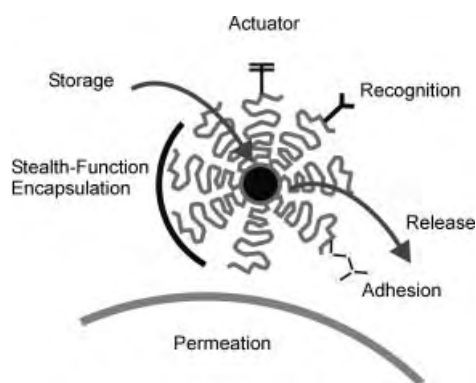


Figure 27. Schematic diagram of biological functions which can be executed by self-organized polymeric structures.

Several of these polymer materials can be integrated into block copolymers. The spontaneous self-assembly leads to functional compartment structures such as micelles, vesicles, and gels which have been tested in many clinical investigations with promising results. They can be applied in prosthetics (artificial intervertebral disks, bone cement), diagnostics (gel electrophoresis), therapeutics (chemotherapy, gene therapy), and sustained drug release.

5.1. Implants

There are three biological prerequisites for implants:

- 1) the mechanical properties such as elasticity and toughness must correspond to those of the tissue to be replaced,
- 2) the implant must not be encapsulated by fibrous tissue, and
- 3) a binding continuous surface should develop between the implant and surrounding tissue.

The mechanical demands on the implants may vary considerably. Intervertebral disks are recognised for their

high elasticity whereas bone cement has to be very hard. Implants can well be adapted to the tissue to be replaced by using microstructured copolymer systems. Telechelic prepolymers such as polyisobutylene (PIB) star polymers with chain-end functionality are preferably used. The material separates into microphases upon growth of the second polymer block. The resulting microstructure corresponds to that of microphase-separated block copolymers, but without having the defined order of the microdomains.

Upon injection of PIB stars with cyanoacrylate end groups at the place of the intervertebral disk to be substituted, the polymerization of the terminal groups is spontaneously initiated by the ambient humidity as is the case with superglue. As a result an elastic PIB matrix chemically and physically cross-linked by the cyanoacrylate microdomains originates, which can replace fractured intervertebral disks.^[152] Broken hip joints are repaired using bone cement out of PIB stars with methyl methacrylate (MMA) end groups. In the application, MMA is added and polymerized and a PMMA matrix cross-linked with PIB microdomains is obtained. The outstanding feature of PMMA (plexiglass) is its hardness. The elastic PIB microdomains make the material less brittle by dissipating mechanical tension (high-impact PMMA).^[153–155]

Biocompatibility of the surface is one of the prerequisites of a successful implantation. Microstructured polymers and gels offer a lot of advantages. PIB stars end-functionalized with 2-hydroxy(methyl methacrylate) (HEMA) or with *N,N*-dimethylacrylamide (DMA) lead to microstructured amphiphilic networks on polymerization with additional monomer (HEMA, DMA). The microstructure resembles that of lyotropic block copolymer phases with domain sizes of 2 to 5 nm, yet without defined domain order ("salt-and-pepper" morphology).^[156–158]

Elastic implants out of PIB-PHEMA and PIB-PDMA show low protein absorption because of their hydrophilic surface. Figure 28 depicts the protein absorption from blood plasma compared with conventional materials such as glass, polyethylene (PE), and polydimethylsiloxane (PDMS).^[159] Above all, the low values of fibrinogen adsorption prove the good blood compatibility of such materials. Fibrin adsorption should be low so as to avoid the blocking of capillaries, which often have diameters of only few millimeters. Biodegradable components can also be incorporated into amphiphilic gels, for example, in materials made out of PEO-PPO-PEO/PLac^[160, 161] or PI-PLac,^[162] which can also be used as biodegradable flexible fibers.

Table 6. Functional principles of polymeric biomaterials.

Function	Action principle	Example
stealth	hydrophilicity	PEO, polyacrylic acid, polysaccharide, poly(vinyl alcohol), PVP
chemically inert	$\gamma < 30 \text{ N m}^{-2}$	PDMS, teflon, PIB, PU
biodegradable	hydrolytically or enzymatically degradable polyester	PGly, PLac, PA
cell adhesion		adhesive glycoproteins, fibronectin
cell detection	vectors	immunoglobulins (IgG), RGD sequence
cell permeation	membrane compatibility	PEO, lipids
salt actuator	polyelectrolytes	PAAc, poly-L-Lysine
temperature actuator	phase separation	PPO, PNIPAM
pressure actuator	phase transition through ultrasound	metastable micelles
glucose actuator	complex formation	tetraphenylene boronic acid

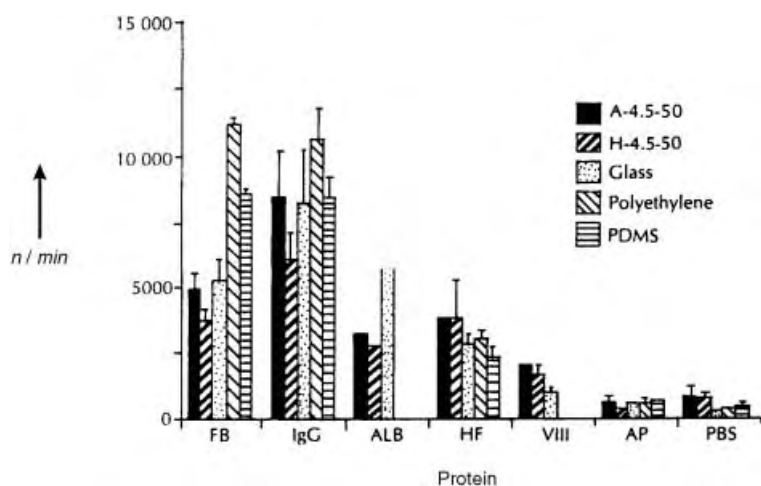


Figure 28. Protein absorption of amphiphilic gels (A, H) compared with conventional materials (glass, PE, PDMS).^[159] FB: fibrinogen, IgG: immunoglobulin G, ALB: albumin, HF: Hageman factor, VIII: Willebrand factor, AP: alphetetoprotein, PBS: phosphate-buffered salt solution (control experiment). The low values of the fibrinogen adsorption (FB) indicate good blood compatibility.

5.2. Gel Electrophoresis

Gel electrophoresis is one of the most important analytical methods of molecular biology. In most cases, polyacrylamide gels are used as stationary phase. Efficient separation media for the analysis of biopolymers are intensively being developed. The planned classification of acrylamide into a special poison category throughout the European Community requires an urgent search for alternative separation media. In principle, the chromatographic separation of a substance mixture results from enthalpic and entropic interactions with a stationary phase. When lyotropic phases of amphiphilic block copolymers are used as the stationary phase, the substances enter an enthalpic distribution equilibrium between the micelle shells and the eluant. Since the hydrophobic domains of lyotropic block copolymer phases are rather large, it is possible to solubilize biopolymers such as polypeptides and polynucleotides. Distribution equilibria between dextrane solutions and lyotropic PEO-PPO-PEO phases (P105, F68) have been thoroughly investigated. Dextranes are water-soluble polysaccharides which are applied in chromatography as column materials or blood plasma expanders. Hydrophilic proteins such as lysozyme, bovine serum albumin, and cytochrome C remain in the aqueous phase whereas hydrophobic membrane proteins such as bacteriorhodopsin and gramicidin D accumulate almost completely in the hydrophobic PPO phase.^[163, 164] Slightly hydrophobic substances such as tryptophane and phenylalanine oligopeptides and cytochrome b(5) are distributed, depending on salt concentration and temperature, in both phases.^[165]

This variable accumulation or partitioning of biomolecules in lyotropic block copolymer phases can be made use of in capillary gel electrophoresis (CGE). Detailed studies on this matter have been carried out with PEO-PPO-EO (F127) which forms cubic liquid crystalline gel phases at a concentration of 18–30% and a temperature of 20–30°C (Figure 10). Chu and co-workers^[166, 167] carried out a detailed structural analysis with light, X-ray, and neutron diffraction of

F127 in buffer solution as used for DNA separation. A temperature decrease to less than 5°C leads to a reversible gel/sol transition to solutions of low viscosity which are easy to fill into the CGE capillaries, thus offering advantages for technical applications. The separation of various nucleic acids, oligonucleotides, DNA fragments, and of plasmid DNA have been described.^[168]

The separation can be optimized to produce the best possible results by varying the polymer concentration and the temperature. Conditions such as those necessary for DNA sequence analysis or oligonucleotide therapy can be achieved (Figure 29). Single nucleotides in dT(12–18) and dT(19–24) standards are separated with baseline separation within eight minutes.^[169] The block copolymer gel does not only operate as the separating phase but also as a coating which suppresses the electroosmotic flux at the inner wall of the quartz capillary. The advantage of block copolymer gels becomes evident in their high selectivity and solubility, the fact that it

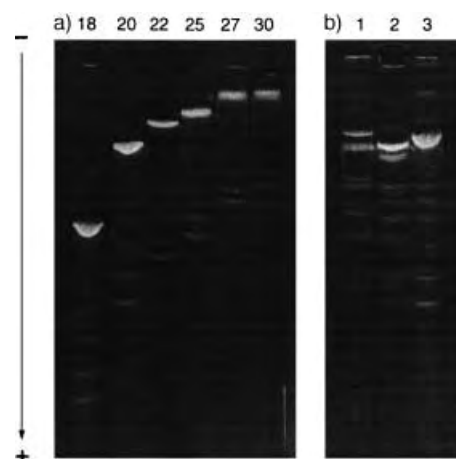


Figure 29. Electrophoretic separation of double-stranded DNA fragments in a lyotropic block copolymer phase.^[171] a) $N \times 123$ bp DNA in 18, 20, ..., and 30% solution. b) DNA restriction fragments.

is possible to exchange the stationary phase (in contrast to the cross-linked hydrogels), and the convenient column handling. High reproducibilities of the electrophoretic migration times ($< 2\%$)^[170] allow miniaturization and automation of CGE.^[171]

One problem still remains unsolved, namely, elution in media which break hydrogen bonds, for example, in concentrated urea/formaldehyde solutions. These are used to separate the two complementary DNA strands. The solubility of the block copolymers differs so strongly in these media that it is often not possible to maintain the structure of the superlattice. The latter may, however, be stabilized by methods as described in Section 3.6.

5.3. Drug Delivery

Currently research is increasingly being done in the field of drug delivery and drug targeting on a molecular level. Fresh

impetus is given in particular by the progress made in biotechnology and immunology supplying new classes of highly effective therapeutics such as polypeptides, oligonucleotides, and genes. For these high molecular weight active agents new delivery and targeting mechanisms have to be developed. At the same time the discovery of monoclonal antibodies and an increased knowledge of cellular receptors led to new approaches in this field. To transport an active agent specifically to the target at the right moment and over a predetermined period of time is the goal for scientists.

Macromolecules offer a wide variety of possibilities as specific transportation systems in biology and medicine. They allow a large number of functions in a molecule to be combined. Small molecules cannot cope with such a number of functions.^[172] One problem when using high molecular weight active ingredients is proteolytic decomposition, for example, upon oral administration, and in low permeation through cellular membranes. For this reason such substances have mostly to be administered parenterally, that is, intravenously, subcutaneously, or intramuscularly. Their tissue specificity is first confined to the cells of the reticuloendothelial system (RES) which recognizes them as foreign microparticles and transports them to the liver and spleen. Their biodistribution can, however, be regulated by surface modification, for example, by introducing PEO (stealth systems) or monoclonal antibodies (site-specific targeting). The proteolytic decomposition can be suppressed by encapsulation, for example, in liposomes, polymers, or polysaccharides. By this means, the residence time, bioavailability, and permeability of polymeric active agents can be increased.

After the polymers have been transported to the place of their target, the active agent is released. This takes place either by depolymerization or by splitting the active component from the polymer, by a swelling of the polymer and resulting release of the active ingredient, or by effusion of the active agent. For control purposes an actuator function may be of use which triggers the release of the active agent depending on local conditions such as salt concentration, temperature, and pH value. Amphiphilic polymers and their association structures are of increasing interest as carriers of active ingredients.^[173] An example of such a carrier system is shown in Figure 27.

5.3.1. Micellar Systems

Block copolymer micelles are being investigated in many research groups as carriers of hydrophobic active agents and genes. Their core/shell structure resembles that of lipoproteins and viruses. The micelle shell causes the interaction with proteins and cells. These interactions decide on the biodistribution of the active component. Endogenic ligands with target function can be bound at the end of the chain of the outer polymer block. Such “intelligent” carriers are able to select their targets. The binding and release of the active agent are, however, determined by the polymer block in the micelle core. Various studies provide evidence of a long residence time of block copolymer micelles in blood proving the applicability of block copolymer nanoparticles as carriers

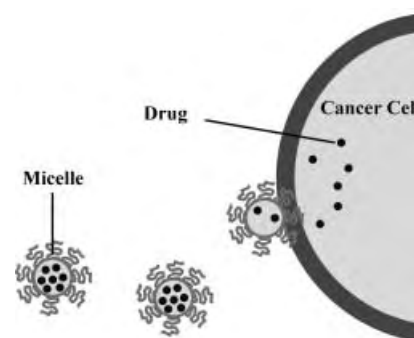


Figure 30. Chemotherapy with block copolymer micelles transporting drugs into the tumor cell.

for the specific transport of active components (site-specific drug delivery; Figure 30).^[174]

The idea of using block copolymer micelles as carriers of active agents results from studies carried out by Ringsdorf and co-workers in 1984^[175] who investigated micelles of poly(L-lysine-*b*-ethylene oxide)(PLys-PEO).^[176] The active components can be bound with labile peptide bonds. Protease, which occurs in increased concentration in many tumor types, is able to break this bond. Later Kataoka and co-workers were able to prove with a similar system, poly(asparaginic acid-*b*-ethylene oxide) (PAsp-PEO),^[177] that anticancer drugs can physically be solubilized in the micelle core. Such polypeptide PEO block copolymers are very well suited as carriers of active components. PAsp solubilizes large quantities of drugs and, being a polypeptide, is biodegradable. PEO is water soluble, chemically stable under physiological conditions, and reduces the antigenic effect of the block copolymer/agent conjugate. Ligands with target function can be bound to the OH end groups of the PEO block.^[178–181]

In water the PAsp-PEO block copolymer micelles have a diameter of approximately 60 nm. As a result of this size, neither renal filtration nor uptake by the RES occurs. Hence the micelles circulate in the blood stream for a long time. The low critical concentration of micelle formation (cmc) means that block copolymers generate micelles even when highly diluted in blood. The low concentration of unimers are excreted by the kidneys. As an example the loading of PAsp-PEO with doxorubicin (DOX) and the corresponding anticarcinogenic effect were systematically investigated.^[177, 180–185] In a few cases it was possible to completely remove subcutaneous tumors of mice through the increased doses with this kind of chemotherapy (Figure 31).^[186] For many kinds of tumors the specific transport to the tumor cells can be accomplished through the increased vascular permeability of diseased tissue.

PEO-PPO-PEO micelles as conjugates with anthracyclin antibiotics (doxorubicin, Ruboxyl, EPI) have also been applied in chemotherapy with the result that life expectancy increased by more than 150 % and the growth of the tumor was inhibited by more than 90 %. Some conjugates caused the tumors to completely disappear.^[187] In these cases especially, the influence of ultrasound increased the absorption of the active agent by the tumor cells. Encapsulation and subsequent focused sonication of micelle conjugates represent an addi-

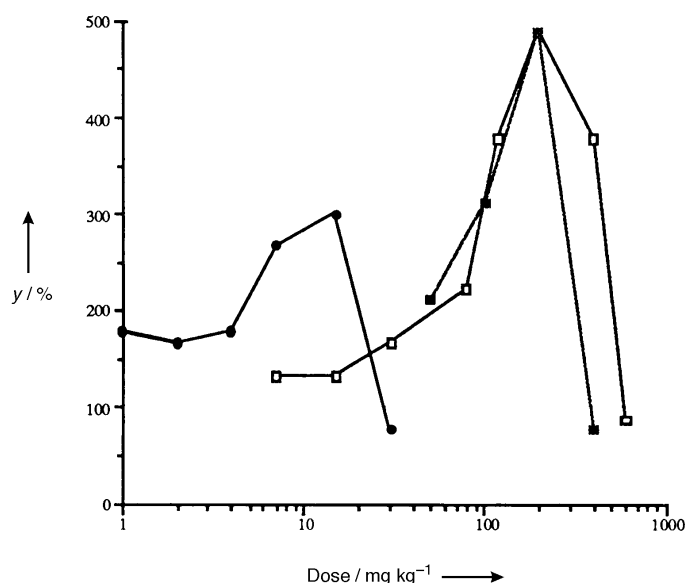


Figure 31. Increase of life expectancy y after chemotherapy with block copolymer micelles:^[186] ● = DOX, □ = PEO-PAsp/DOX 4–17, ■ = PEO-PAsp/DOX 5–80. The block copolymer conjugates can be administered at higher doses thus achieving a higher antitumor effect. Doxorubicin (DOX) was used. $y = 100$ corresponds to life expectancy without chemotherapy.

tional way of gentle transport of active agents and specific release in tumors.^[188, 189]

The high activity of PEO/agent conjugates is closely connected with their special transport behavior through biological barriers. PEO influences the microviscosity and permeability of cell membranes.^[190] This is the result of a special property of PEO: at a high degree of hydration in aqueous media PEO is hydrophilic, while at a low degree of hydration in hydrophobic environment it is, however, hydrophobic. Thus, PEO can dehydrate at hydrophobic surfaces and can be transported into or through these boundary surfaces. The penetration and accumulation of PEO in hydrophobic lipid layers was proved by X-ray reflection studies.^[191]

5.3.2. Multidrug Resistance

The development of a multidrug resistance (MDR) represents a considerable problem in the successful treatment of cancer by chemotherapy. Although many types of cancer recede in the beginning, recurrence often occurs and is accompanied by a resistance against a wide variety of structurally different drugs. An overexpression of the MDR1 gene which encodes the plasma membrane protein P-gp (P glycoprotein) is mainly responsible for this situation. This transport protein transports drugs out of the tumor cell thus causing the resistance against these cytotoxins. A short application of usual chemotherapeutics already often leads to a quick increase in the gene expression.

In order to avoid this, active agents are being developed which block P-gp, thus guaranteeing an accumulation of the drugs in the cancerous cell. PEO-PPO-PEO micelles have proved to be surprisingly efficient. By using PEO-PPO-PEO/daunorubicin conjugates, already resistant cancer cells showed a dramatic increase (by a factor of 700) in the

daunorubicin activity (“hypersensitization”). The ID_{50} dose of $25 \mu\text{g mL}^{-1}$ of free daunorubicin was decreased to $0.16 \mu\text{g mL}^{-1}$ for block copolymer/conjugated daunorubicin. An increase of activity by a factor of 20–1000 caused by the block copolymer was also observed with other drugs such as doxorubicin, epirubicin, vinblastin, and mitomycin C. This procedure in combination with chemotherapeutic drugs could well be used to overcome MDR.^[192–194]

5.3.3. Blood–Brain Barrier

The blood–brain barrier hinders detrimental substances from penetrating the extremely sensitive brain. The permeability of the capillary wall is selectively decreased for many substances, especially for electrically charged molecules. This effect corresponds to other blood–tissue barriers of the organism (for example, blood–liver, blood–placenta), but it is more effective. The function of the blood–brain barrier is to protect the central nervous system against detrimental chemical influences as well as to maintain a high concentration of the substances important for the metabolism of the central nervous system, such as glutamic acids, K^+ , and phosphate.

In vitro experiments showed that nonionic block copolymers such as PEO-PPO-PEO proved to be surprisingly effective with regard to the transport of active agents through the blood–brain barrier. Monolayers of brain capillary endothelial cells served as a model system. In the presence of block copolymers a much more effective transport and the accumulation of the fluorescence marker rhodamin 123 into the cells were observed. The investigations made it evident that the increased effectiveness has also to be attributed to an inhibition of the P-gp protein and to a more effective transport via micelles or vesicles through the cell membrane.^[195] Increased transport and accumulation have also been observed in regard to the penetration of intestinal epithelium cells.^[196]

5.3.4. Lyotropic Phases as Drug Reservoirs and Actuators

Lyotropic phases (gels) can also be used as delivery systems. They are either directly administrated, as in the case with antibiotics,^[197] rheumatics,^[198] or insulin,^[199] or they are dispersed as microparticles. The latter, with a diameter of approximately $5 \mu\text{m}$, are frequently produced by means of a w/o/o emulsion/solution extraction technique. Adsorption capacity and release profiles have been studied in detail for some systems. Up to 40% ovalbumin, for example, can be adsorbed in microparticles of a PEO-PPO-PEO/PLGA conjugate. With a release capacity of up to $3 \mu\text{g mg}^{-1}$ per day, linear release profiles are observed in vivo over a period of 25 days.^[200] The release of insulin^[201] as well as of vaccine formulations from microparticles^[202] are also being investigated.

In regard to controlled release, there is a wide variety of applications of gels and microparticles which react to environmental conditions such as temperature, salt concentration, or pH value (actuators; Table 7). Sensitivity to these factors can be achieved by conjugation with other polymers or by the use of special ligands. As an example, the PEO-PPO-PEO/

Table 7. Biological functionalization of block copolymer micelles and microparticles.

Particle	Core block	Shell	Active ingredient	Remarks
micelles	PPO, PLys, PAsp, PLac	PEO	DOX, ruboxyl, EPI, daunorubicin	HL-60 cancer cells, subcutaneous cancer cells
	PPO	PEO	daunorubicin, DOX, EPI, vinblastin, mitocytin	multidrug resistance
	PPO	PEO	rhodamine	blood–brain barrier
	PAsp	PEO	fluorescein	permeation into endothelial cells
simplex micelles	P4VPEtBr	PEO	plasmide DNA	gene transfection
	polyspermine	PEO	oligonucleotide	herpes virus inhibition
	PAsp	PEO	lysozyme	
microparticle/gels	PEI	PEO	plasmid DNA	gene transfection
	PPO	PEO	antibiotics	wound treatment
	PPO	PEO	diclofenac	antirheumatic treatment
	PIB	PHEMA		
	PU/PPO	PEO		
	PLac/PGly/PPO	PEO	ovalbumin	
	PAAc/PPO	PEO	steroid hormone	
		PEO	insulin	glycemia
	polyurethane/PPO	PEO		
	plasmide DNA/lipid/PPO	PEO		gene transfection
	PPO	PEO		phagocyte resistance, radiodiagnostic, imaging, bone marrow, spleen, lymph nodes

polyacrylic acid conjugates can easily be obtained by spontaneous complex formation through the generation of hydrogen bonds and hydrophobic interactions.^[203, 204] They have a pH value, salt concentration, and temperature-actuator effect. By specific variation of these parameters it is possible to shrink, swell, or dissolve the gels.^[205, 206] Proteins, steroid hormones, and insulin, for example, have been conjugated with these gels and purposefully released.^[207] Glyco-responsive systems can be obtained through the binding of phenylboronic acid, which forms covalent complexes with polyols such as glucose.^[208] When the local glucose concentration decreases glucose is released out of the microparticles so as to maintain the complexation equilibrium. Model conjugates of PEO-PPO-PEO/polyacrylic acid/concanavalin for a glucose-responsive insulin release are being developed.^[209]

5.4.1. Gene Therapy

The results of the international humane genome project, which has meanwhile been concluded, holds out the prospect that it will be possible to cure diseases through the use of genetic engineering and therapy. There is a wide therapeutic potential for gene therapy; more than 4000 human genetic diseases are known and practically every illness is fundamentally affected by genetic factors.

In gene therapy genes are introduced into the cells to replace a lacking or defective gene or to block a faulty one. Genetically modified viruses (retroviruses) are used in which the gene sequence for multiplying has been taken out and replaced by foreign DNA. They integrate their genome as a part of their lifecycle into the genetic material of the host cell (transfection). The disadvantages of genetic therapy with retroviruses are a high antigen reaction, the risk of recombination with wild-type viruses, and cell damage caused by viral vectors.

Therefore, scientists are searching for synthetic, nonviral gene-transfer systems using plasmide DNA which can be produced on an industrial scale by means of modern

fermentation technology. Plasmids are small, circular extrachromosomal DNA molecules which are able to replicate independently in a host cell. Accumulation and transport of plasmid DNA can take place with the aid of cationic particles. As a result of electrostatic attraction, the latter form stable complexes with the negatively charged plasmid DNA. Liposomes from positively charged lipids are used for complex formation. The use of polycations also leads to the spontaneous formation of stable polyelectrolyte complexes (simplexes). Soluble simplexes prepared from plasmid DNA with different polycations exhibited increased plasmid penetration in cells. This is a new approach to effective transfection of genetic materials in vivo.^[210]

The unsatisfactory low solubility of simplexes can be improved considerably by using polycation-PEO-block copolymers. Studies carried out with simplexes made from PMAc-PEO and poly-4-vinyl-*N*-ethylpyridinium bromide (P4VPEtBr) showed that water-soluble stoichiometric complexes are formed which have a well-defined micellar structure with a core of the simplexes surrounded by a PEO shell. The micelles dissolve upon addition of salt (Figure 32).^[211–213] To address particular cell types, the micelle can be conjugated with a ligand which is recognized and absorbed only by cells with the corresponding receptor. This was, for example, achieved by the covalent binding of a glycoprotein with exposed galactose residues to a poly-L-lysine which complexes negatively charged DNA.

Studies of the therapeutic effect were, for example, carried out with polyspermine-PEO block copolymers which spontaneously form water-soluble complexes with oligonucleotides.^[214] A DNA segment which inhibits the reproduction of the herpes simplex virus 1 served as the oligonucleotide. Titration after 22 and 39 hours after the infection showed that the complex inhibits the reproduction of the virus to below the detection limit. The free oligonucleotide had only a short-term effect.^[215] Absorption of plasmid DNA and cell transfection can be further increased when PEO-PPO-PEO block copolymers which modify the membrane properties are added at the same time.^[216, 217]

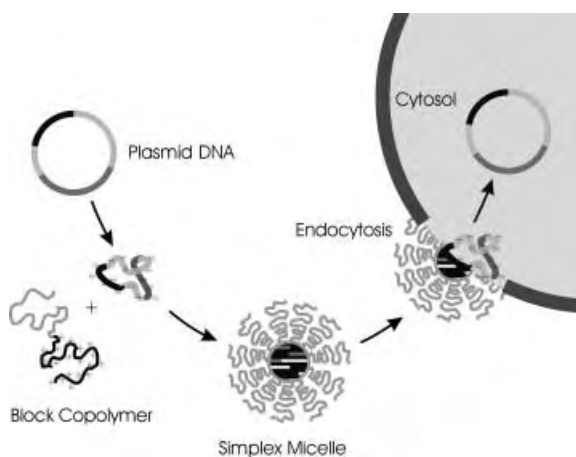


Figure 32. Encapsulation and transport of plasmid DNS in micelles. After transport into the cell the DNA is released as a result of the high local ionic concentration.

6. Conclusion and Outlook

Self-organizing systems offer a wide variety of methods for structuring and functionalizing materials on the nano- and mesoscopic length scale. A large number of superlattices can be realized with the help of quite simple molecules. Of special interest in this respect are macromolecules: their fundamental mechanisms of self-organization and their good material properties are known and it is possible to implement several functions on one macromolecule. This process leads to many approaches for the preparation of novel inorganic materials and of materials with biological function. These concepts can in many cases be transferred to polymers, such as graft copolymers and latices, which can more easily be prepared on a technical scale. This opens up ways for an economic scale-up of the synthesis.

In some cases it has already become possible to synthesize structure hierarchies. In nature hierarchical structures are the basis of the spacial and temporal organization of the chemical processes in a cell. The formation of the secondary structure $\leftrightarrow$ tertiary structure $\leftrightarrow$ quaternary structure of proteins which all are predetermined by the primary structure or—in the case of muscles—the hierarchy of actin/myosin filament $\leftrightarrow$ myofibril $\leftrightarrow$ muscular fiber may serve as examples for this. Only the simultaneous coordination of all structure units leads to muscle contraction. It will still take quite a lot of time until the structural and dynamic organization in polymeric systems will be mastered in a similarly perfect way. Until now results of controlled coordination have been achieved best with actuators. In many cases it will not be either a bottom-up or top-down strategy, but the integration of both procedures which will lead to functional structures.

In the years to come the question of how to address self-organized systems will become more and more important. This involves, for example, the control of transmission and storage of electrical and magnetic signals in self-organized architectures. The transmission and storage of information in neurons proves that in nature this is in principle possible. The processing of information takes place through complicated

structure hierarchies, for example, neurotransmitter $\leftrightarrow$ synapse $\leftrightarrow$ axon $\leftrightarrow$ neurone network. The binding of such self-organized information structures to the outside world through a defined interface represents a problem which is being dealt with in quite another connection: Some research teams are working on the binding of neurons to transistors and external circuits.^[218, 219] Approaches to the development of self-organized information structures, such as signal transmission and storage in brains, represent a challenge as well as a fount of inspiration.

The potential of applied technology resulting from the investigation of nano- and mesoscale materials is beyond controversy. In 2000 the US President originated the National Nanotechnology Initiative with an investment volume of more than US\$ 500 million. There are similar activities in Japan and in Europe.^[220] In all cases, the necessary training of scientists in interdisciplinary fields of chemistry, physics, biology, medicine, and materials research is promoted. Multi-disciplinarity is a characteristic feature of this kind of research. It has become evident that new routes at junctions of traditional specific fields can be very promising, as they often represent the starting point for novel and unconventional approaches.

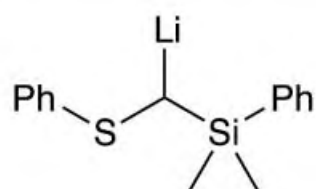
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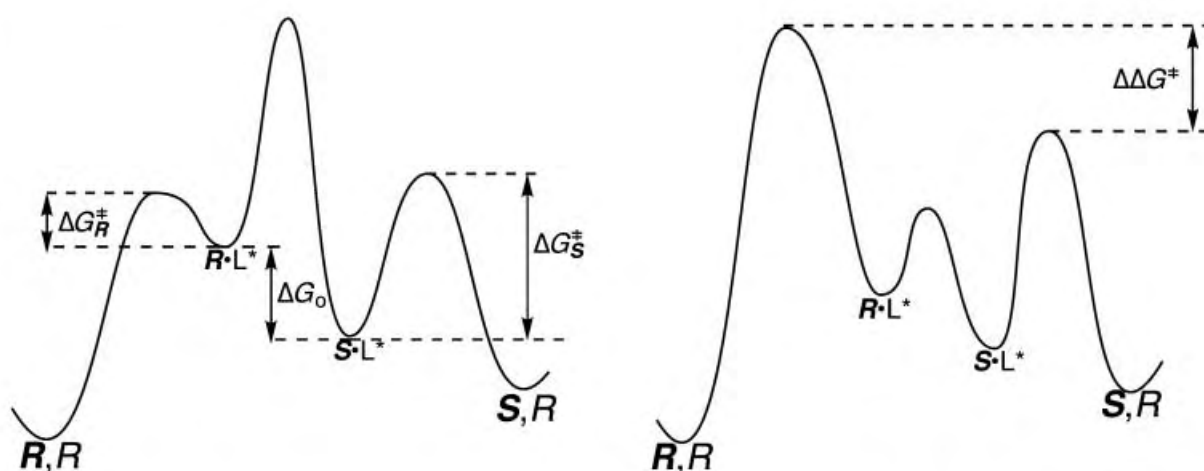
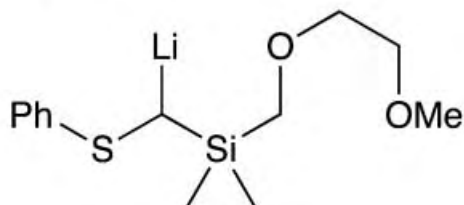
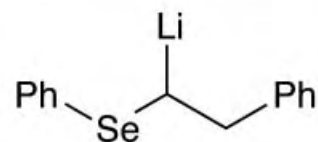
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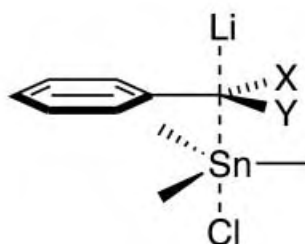
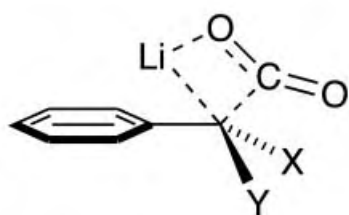
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Examples of organolithium structures which have contributed to our understanding of configurational inversion pathways



Relative rates of inversion and electrophilic substitution can be probed by using the Hoffmann test for configurational stability



Retentive vs. invertive electrophilic substitution determines product stereochemistry

Configurational Stability and Transfer of Stereochemical Information in the Reactions of Enantioenriched Organolithium Reagents

Amit Basu* and S. Thayumanavan*

The conversion of a prochiral methylene group into a stereogenic center by means of a lithiation/substitution sequence has emerged as a powerful synthetic transformation over the past 15 years. This reaction proceeds via a chiral organolithium intermediate, and the stereochemical fidelity of the overall reaction sequence is intimately dependent on the stereochemical behavior of the chiral organolithium as well as on the rate and stereochemical

sense of the electrophilic substitution step. Chiral organolithium reagents were first reported by Letsinger, Curtin, and Applequist half a century ago. The lithiated intermediates in these early studies were not highly configurationally stable, and applications in stereoselective synthesis were not immediately forthcoming. The two decades that followed the 1980 report by Still and Sreekumar of a configurationally stable α -oxyorganolithium were

marked by an increased interest in these reagents. As the synthetic applications of chiral organolithium reagents have grown, so have accompanying mechanistic studies of these intermediates which serve as the basis for this review.

Keywords: asymmetric synthesis • configuration determination • enantioselectivity • electrophilic substitution • lithium

1. Introduction

The synthetic utility of chiral organolithium intermediates continues to provide the impetus for the development of new pathways for the stereoselective generation and subsequent reactions of these reagents. The synthesis (Scheme 1) involves conversion of an achiral starting material **R1** into one of two enantiomeric products **P1** or *ent*-**P1**. The stereoselectivity of the transformation is dependent on three factors:

- a) the selectivity of formation of the stereoisomeric intermediates **C1** and *epi*-**C1**;
- b) the rates of epimerization of **C1** and *epi*-**C1** relative to their rate of reaction with electrophiles;
- c) the stereochemical course of the electrophilic substitution.

Changes in these variables can alter the stereochemical outcome of the reaction. Three limiting pathways are available for the transfer of stereochemical information:

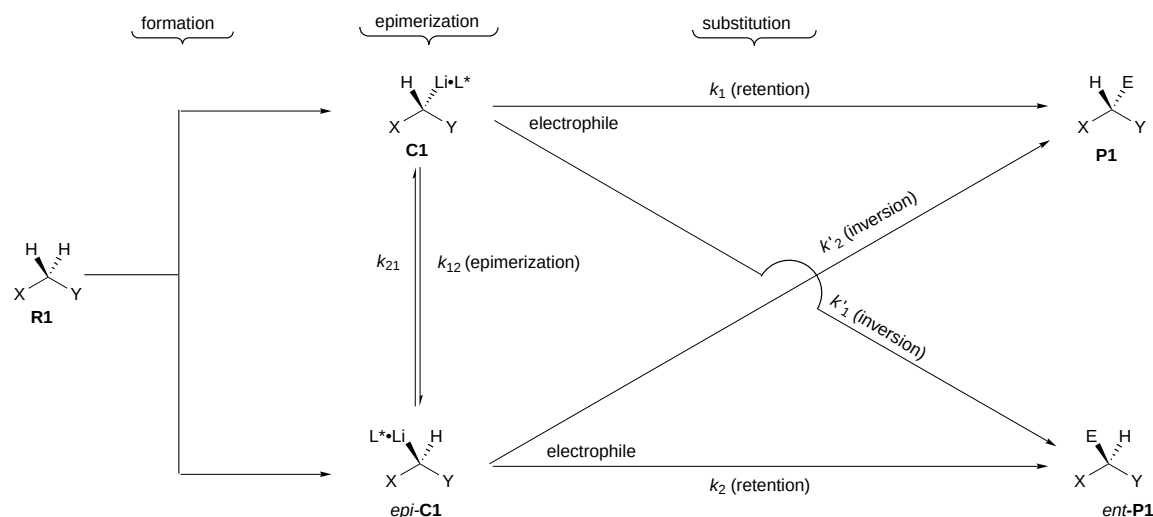
- a) *asymmetric deprotonation*: the selective formation of either **C1** or *epi*-**C1** by enantioselective proton abstraction

from **R1** to generate a configurationally stable intermediate;

- b) *dynamic kinetic resolution*: the lithiated intermediate is configurationally labile (i.e. **C1** and *epi*-**C1** are in rapid equilibrium), and stereoselectivity arises as a result of the differences in the transition state energies of electrophilic substitution for each diastereomeric intermediate;
- c) *dynamic thermodynamic resolution*: the configurational stability of the diastereomeric intermediates is dependent on temperature, and stereoselectivity is dependent on the ratio of the two complexes.

Knowledge of the configurational behavior of the diastereomeric intermediates is crucial for identifying and understanding the reaction pathway. However, a detailed understanding of the origins of configurational stability remains unclear. The extent of the configurational stability and the mechanisms of inversion are very much dependent on the particular substrate. We are not aware of any example of an acyclic, sp^3 -hybridized, nonheteroatom-containing organolithium compound that exhibits synthetically useful configurational stability under standard reaction conditions. The presence of a heteroatom within the molecule, whether it is adjacent to the lithium-bearing carbon atom or at some distal center, can significantly influence the stereochemical properties of the organolithium compound. A large variety of highly functionalized and synthetically useful chiral organolithium reagents have been developed in the past two decades.

[*] Prof. Dr. A. Basu
Department of Chemistry, Brown University
Providence RI 02912 (USA)
Fax: (+1) 401-863-2594
E-mail: Amit_Basu@brown.edu
Prof. Dr. S. Thayumanavan
Department of Chemistry, Tulane University
New Orleans, LA 70118 (USA)
Fax: (+1) 504-865-5596
E-mail: thai@tulane.edu



Scheme 1. Overview of steps involved in the lithiation and substitution of prochiral methylene groups.

In this review, we discuss these intermediates, their configurational stability, as well as the stereochemistry of the electrophilic substitution step. Initially (Section 2), we focus on the chemical and physical techniques that are used to probe the epimerization of enantiomeric/diastereomeric intermediates. Section 3 is a compendium of recent developments that involve the use of chiral organolithium reagents, and is organized on the basis of the substitution pattern adjacent to the organolithium center. We have restricted our focus in this section primarily to enantiomeric organolithium species. However, we mention diastereoselective reactions insofar as they provide unique and interesting examples of mechanistic phenomena that can be extended to the reactions of enantiomeric organolithium species. We conclude (Section 4) with a reexamination of the stereochemical irregularities that are frequently associated with the electrophilic substitution step.

We do not explicitly discuss the various methods for the selective generation of stereoisomeric intermediates **C1** and

epi-C1, except for a few examples and relevant references. Although (–)-sparteine features prominently throughout the article, this is not a review of (–)-sparteine-mediated chemistry. The reader who is specifically interested in (–)-sparteine-assisted methodologies or coverage of synthetic applications is referred to several recent reviews.^[1–4] Furthermore, the synthetic applications of these organolithium intermediates are beyond the scope of this article.

2. Spectroscopic and Chemical Methods for Determining Configurational Stability and Mechanisms of Inversion

2.1. Nuclear Magnetic Resonance Spectroscopy

Much of our understanding of the mechanism of configurational inversion derives from NMR spectroscopy studies of

Amit Basu was bitten by the lithium bug as an undergraduate student at Reed College, where he carried out research with Patrick McDougal and received his B.A. in 1992. This was followed by four more years of lithiation chemistry for his doctoral degree under the guidance of Peter Beak at the University of Illinois, Urbana-Champaign. After postdoctoral studies into the bioorganic chemistry of carbohydrates with Daniel Kahne at Princeton University, he joined the faculty of the Chemistry Department at Brown University in 1999. His current research interests are directed towards investigating the chemical, biological, and materials properties of cell surface carbohydrates.



A. Basu

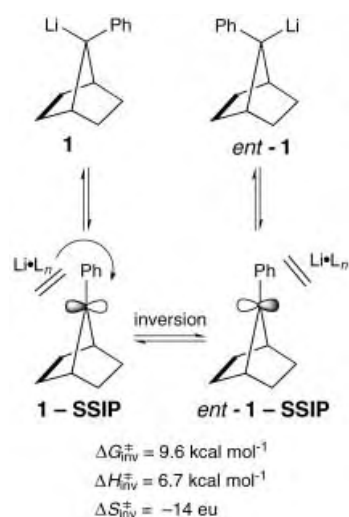


S. Thayumanavan

S. Thayumanavan (“Thai”) received his B.Sc. and M.Sc. in Chemistry at The American College, Madurai, India. He pursued his Ph.D. with Peter Beak at the University of Illinois, Urbana-Champaign. He then carried out his postdoctoral work with Seth Marder at Caltech. In 1999, he joined the faculty of the Department of Chemistry at Tulane University. His current research interests lie in using organic chemistry as a tool for supramolecular organization of functional groups in small molecules and macromolecules, and in utilizing these organized assemblies in areas of chemical, materials, and biological sciences.

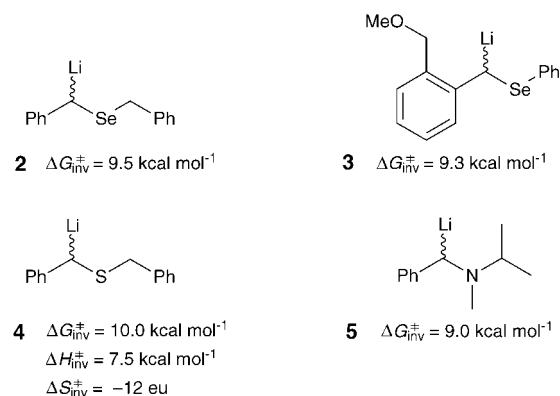
chiral organolithium intermediates, originally performed with primary organolithium reagents that contain diastereotopic marker groups.^[5–7] NMR spectroscopy provides a quantitative description of the barriers for inversion and allows mechanistic information about the process to be inferred. Furthermore, enantioenriched samples are not required, because inversion can be detected by monitoring the dynamic behavior of diastereotopic signals in the molecule of interest. A variety of nuclei, including ^1H , ^{13}C , ^6Li , ^7Li , and ^{31}P have been used to provide structural and mechanistic information on the organolithium intermediate.

Thermodynamic parameters for the inversion of the achiral organolithium **1** (in $[\text{D}_8]\text{THF}$) were determined by means of NMR spectroscopy (Scheme 2).^[8] It has been postulated that inversion occurs by the formation of a solvent-separated ion pair (SSIP) and planarization of the carbanion, followed by rotation of the ring and subsequent ion-pair recombination. The magnitude of the entropy of inversion is consistent with ion separation prior to or during the rate-limiting step.



Scheme 2. Inversion of **1** through SSIP formation.

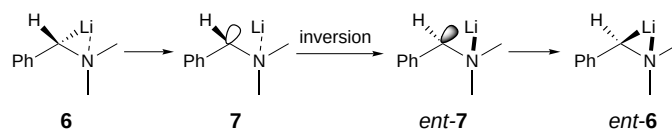
The α -heterobenzyllithium compounds **2–5** have remarkably homogenous inversion barriers despite several structural differences (Scheme 3).^[9] The similar inversion energies of **2** and **3** indicate that the potential coordination of the lithium



Scheme 3. Inversion barriers of α -heteroatom-substituted benzylic organolithium compounds.

center to the heteroatom is not a crucial component of the inversion barrier. Consistent with this hypothesis, the inversion barrier for **4** is not affected by the addition of chelating amines such as pentamethyldiethylenetriamine (PMDTA). Even though there is restricted rotation around the $\text{C}_{\alpha}\text{--C}_{\text{ipso}}$ bond of α -lithio sulfide **4**, the organolithium compound is best characterized as an η^1 species on the basis of the temperature independence of the NMR spectroscopy signals, as well as the absence of a detectable NOE interaction between the lithium atom and the *ortho* hydrogen atom.^[9] In contrast, both the *alpha* and *ipso* carbon atoms of the α -amino organolithium **5** exhibit temperature-dependent chemical shifts which suggests that the η^1 and η^3 structures are in equilibrium. Contrary to the case with **3** and **4**, addition of PMDTA or tetramethylethylenediamine (TMEDA) to **5** increases the inversion barrier. These comparisons reveal that despite the similarities in the magnitudes of the inversion barriers for a variety of α -heteroatom-substituted organolithium compounds, the mechanisms of the configurational inversion can differ. The entropies of activation observed for the inversion of **1** and **4** are consistent with an increased solvation of the lithium atom as it dissociates from the carbanion to form an ion pair. Hoffmann and co-workers have referred to this process as an increased “electrostriction” of the surrounding bulk solvent, that is, an increased solvent organization as a result of the increased dipole of the ion pair.^[9]

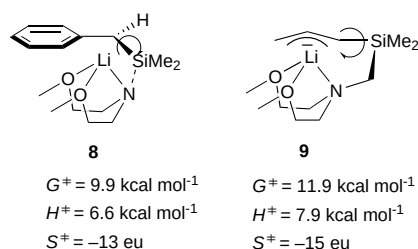
The process of inversion requires the lithium atom to move from one enantioface of a chiral organolithium compound to the other. A possible pathway involves the formation of a separated ion pair, followed by the rotation of the anion prior to reassociation of the lithium, as suggested by Peoples and Grutzner for **1**.^[8] An alternative pathway is a conducted tour mechanism, originally suggested by Cram and Gosser, in which the lithium ion is coordinated to a Lewis basic site in the molecule, and is subsequently delivered to the opposite face of the carbanion.^[10] The crystal structure of α -lithio-*N,N*-dimethylbenzylamine (**6**) indicates that the lithium ion bridges the carbon and nitrogen atoms. This bridged motif has also been observed in additional α -lithio amines by means of NMR spectroscopy.^[11] Such a structure might represent the first step in a “conducted tour” process for an α -hetero organolithium compound which proceeds via the ion pair **7** (Scheme 4).^[12]



Scheme 4. Nitrogen atom facilitated inversion of α -lithio-*N,N*-dimethylbenzylamine.

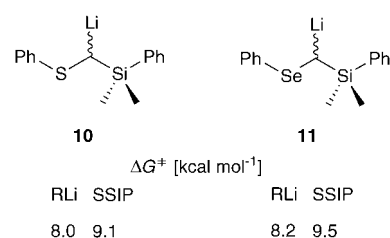
Fraenkel et al. have unambiguously identified an example of the conducted tour mechanism in the dynamic behavior of the benzylic and allylic organolithium reagents **8** and **9**.^[13, 14] Rotation about the C--Si bond places the lithium ion on the other face of the carbanion, formally inverting the configuration of the planar carbanionic center. However, the similarity of the inversion barriers for **2–5**, along with the

lack of a heteroatom effect for the selenides **3** and **4** suggests that intramolecular Lewis base coordination of the lithium ion need not be a dominant factor during inversion (Scheme 5).



Scheme 5. Chelation-assisted configurational inversion of **8** and **9**.

A very different mechanism for the inversion of α -heteroatom-substituted organolithium reagents was reported independently by Hoffmann and co-workers and by Reich et al. in 1993.^[15, 16] The addition of hexamethyl phosphoramide (HMPA) to organolithium compounds **10** and **11** generates spectroscopically characterizable contact ion pairs (CIPs). Titration of the contact ion pairs with additional HMPA generates SSIPs, which were identified by retention of Li–P coupling and the disappearance of Li–H and Li–C coupling in the NMR spectra. Remarkably, the inversion barriers of the SSIPs of **10** and **11** were significantly higher than those of the parent organolithium species themselves (Scheme 6). This observation is inconsistent with a model that involves lithium dissociation and solvation as the rate-determining step.



Scheme 6. Differential inversion barriers for α -thio and α -selenoorganolithium compounds: covalent and SSIP intermediates.

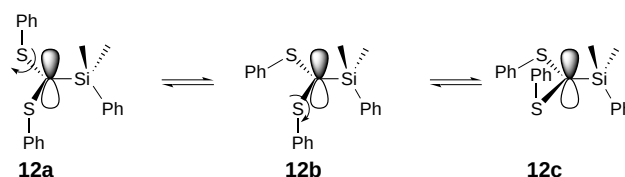
α -Thio-substituted organolithium compounds had long been suggested to be stabilized by $n-\sigma^*$ overlap, thus it was postulated that the rate-determining step for the inversion of **10** and **11** actually involved rotation around the C–S and C–Se bonds, respectively (Scheme 7).^[17] The increased rotation barrier of the SSIP could arise from the repulsion between the carbanion and heteroatom lone pairs, an interaction which is alleviated by the lithium atom in both the contact ion pair and the covalent organolithium species.

Dynamic NMR spectroscopic analysis of related organolithium **12** exhibited coalescence of the signals for the methyl



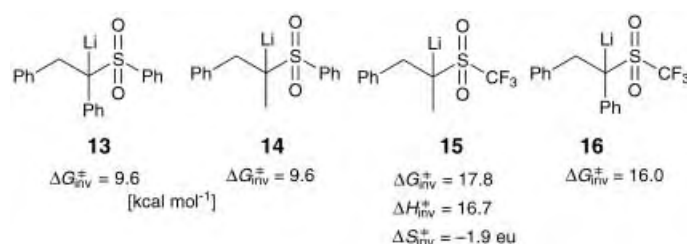
Scheme 7. C–X bond rotation as the rate-determining step (rds) for the inversion of α -thio and α -seleno organolithium compounds.

group, which corresponds to a $\Delta G_{\text{inv}}^\ddagger$ of $13.3 \text{ kcal mol}^{-1}$.^[16] Diastereotopic methyl groups on silicon can be observed only if rotamer interconversion is slow on the NMR time scale, since **12** is achiral if C–S bond rotation is rapid (Scheme 8).



Scheme 8. Formal configuration inversion through sequential C–S bond rotations of **12a**.

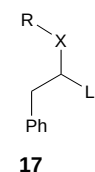
Increasing the steric bulk of the aryl group on the sulfur atom raised the inversion barrier, which is consistent with bond rotation as the rate-determining step. This phenomenon had been documented earlier with chiral α -lithio sulfones by Gais et al.^[18, 19] Trifluoromethyl sulfones **15** and **16** have an inversion barrier which is almost twice as high as that for phenylsulfones **13** and **14**. As before, the higher activation energy is attributed to increased $n-\sigma^*$ overlap caused by the lower energy σ^* orbital of the trifluoromethyl group (Scheme 9).^[20]



Scheme 9. Inversion barriers of tertiary lithiated sulfones.

Hoffmann et al. carried out an extensive NMR study of α -thio-, α -seleno-, α -telluro-, and α -silyl-substituted organolithium compounds **17** (Scheme 10).^[21] In the chalcogen series, an increase in the steric bulk of the aryl group results in a decrease in the rates of inversion, consistent with C–X bond rotation as the rate-determining step. The inversion of α -deuterated **17e** does not exhibit an observable secondary isotope effect, and the inversion barrier for **17e** is not dependent on the solvent. The former indicates that configurational inversion of the organolithium is not the rate-determining step, and the latter result is inconsistent with the formation of a SSIP in the rate-determining step (Table 1).

In contrast, the inversion barriers of the silyl-substituted organolithium compounds do not vary with steric modifications.^[21] This is attributed to the ability of the aryl group to rotate about the $C_{\text{ipso}}-\text{Si}$ bond, thus minimizing the steric impact of the *ortho* substituents. However, when the heteroatom X is sulfur, tellurium, or selenium, $n-\sigma^*$ overlap between the heteroatom lone pair and the aryl ring requires

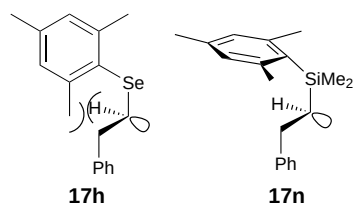


Scheme 10. α -Thio-, α -seleno-, α -telluro-, and α -silyl organolithium compounds (X = S, Se, Te, Si).

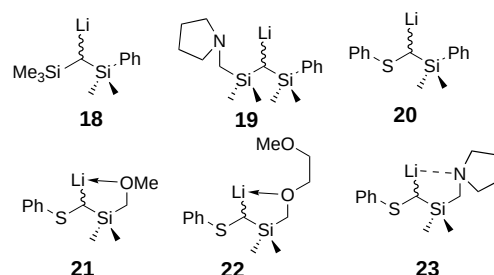
Table 1. Inversion barriers for α -chalcogen organolithium intermediates.

17	X	R	$\Delta G^\ddagger$ [kcal mol ⁻¹]	$\Delta H^\ddagger$ [kcal mol ⁻¹]	$\Delta S^\ddagger$ [eu]
a	S	phenyl	11.3	10.6	-2.7
b	S	<i>m</i> -CF ₃ C ₆ H ₄	11.4	9.3	-8
c	S	<i>p</i> -MeOC ₆ H ₄	11.4	10.2	-4.5
d	S	duryl	> 13.9		
e	Se	phenyl	12.4	11.7	-2.9
f	Se	<i>o</i> -tolyl	12.7		
g	Se	<i>p</i> -tolyl	12.3		
h	Se	mesityl	> 14.3		
i	Se	duryl	> 14.5		
j	Te	phenyl	11.8	10.0	-6.8
k	Te	duryl	13.9	14.7	3.0
l	SiMe ₂	methyl	12.6	11.3	-5
m	SiMe ₂	phenyl	11.8	12.4	2.0
n	SiMe ₂	mesityl	11.8	11.1	-2.6
o	SiPhMe	phenyl	11.7	9.7	-7.9
p	SiMe ₂	phenyl	11.9	7.0	-18.4

that the carbanion lone pair be positioned in a synclinal orientation to the nonbonded electrons on the heteroatom ring in the transition state of enantiomerization. This back-bonding type of interaction alleviates the energy cost of eclipsing the lone pairs, but imposes rotational restrictions on the C_{ipso}-X bond. In contrast, the arylsilane can twist out of the plane and avoid unfavorable steric interactions (Scheme 11).

Scheme 11. Steric interactions in the inversion of α -thio and α -silyl organolithium compounds.

The effect of heteroatom substitutions on the inversion barriers of α -silyl and α -thio organolithium compounds has been examined by using similar NMR spectroscopy methods.^[22] The bis-silyl organolithium compound **18** has a $\Delta G^\ddagger_{\text{inv}}$ of 11.2 kcal mol⁻¹, whereas the SSIP formed upon addition of 4 equivalents of HMPA has a corresponding barrier which is less than 7 kcal mol⁻¹. The presence of a coordinating heteroatom as in **19** does not have a significant effect on the inversion enthalpy $\Delta G^\ddagger_{\text{inv}}$ of the CIP, but significantly reduces the $\Delta S^\ddagger_{\text{inv}}$ term. Formation of the SSIP upon addition of 4 equivalents of HMPA reduces the barrier of **19** to less than 7.0 kcal mol⁻¹. These results are consistent with a model of inversion that involves the dissociation and solvation of the lithium atom in the transition state of inversion. Coordination of the lithium ion to a nitrogen atom slightly decreases the value of $\Delta G^\ddagger_{\text{inv}}$, but the entropic contribution is significantly reduced. The small values of $\Delta S^\ddagger_{\text{inv}}$ suggest that the nitrogen atom plays a role in delivering the lithium ion to the correct face of the newly inverted carbanion. In contrast, the $\Delta G^\ddagger_{\text{inv}}$ values for the thio-substituted organolithium compounds **20**–**23** (Scheme 12, Table 2) increase when intramolecular coordination is possible. Since the transition state for the inversion of **22** and **23** involves bond rotation and not lithium

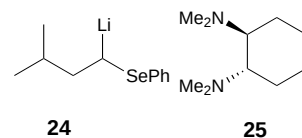
Scheme 12. Effect of coordinating heteroatoms on the inversion barriers of α -silyl and α -thio organolithium compounds.

coordination, the increased $\Delta G^\ddagger_{\text{inv}}$ values relative to **20** may represent better stabilization of the ground state in these species. In cases where $\Delta S^\ddagger_{\text{inv}}$ was determined, the values were found to be low which is consistent with a rate-determining step that involves bond rotation.

Table 2. Effects of the heteroatom on the inversion barriers of α -silyl organolithium intermediates.

Compound	$\Delta G^\ddagger$ [kcal mol ⁻¹]	RLi $\Delta H^\ddagger$ [kcal mol ⁻¹]	$\Delta S^\ddagger$ [eu]	SSIP $\Delta G^\ddagger$ [kcal mol ⁻¹]
18	$\Delta G^\ddagger = 11.2$	$\Delta H^\ddagger = 10.1$	$\Delta S^\ddagger = -6.3$	< 7.0
19	$\Delta G^\ddagger = 10.7$	$\Delta H^\ddagger = 10.5$	$\Delta S^\ddagger = -1.3$	< 7.0
20	$\Delta G^\ddagger = 8.0$	$\Delta H^\ddagger = 7.9$	$\Delta S^\ddagger = -0.5$	9.5
21	$\Delta G^\ddagger = 10.0$			9.4
22	$\Delta G^\ddagger = 9.3$			9.6
23	$\Delta G^\ddagger = 10.5$	$\Delta H^\ddagger = 9.8$	$\Delta S^\ddagger = -3.6$	≥ 9.4

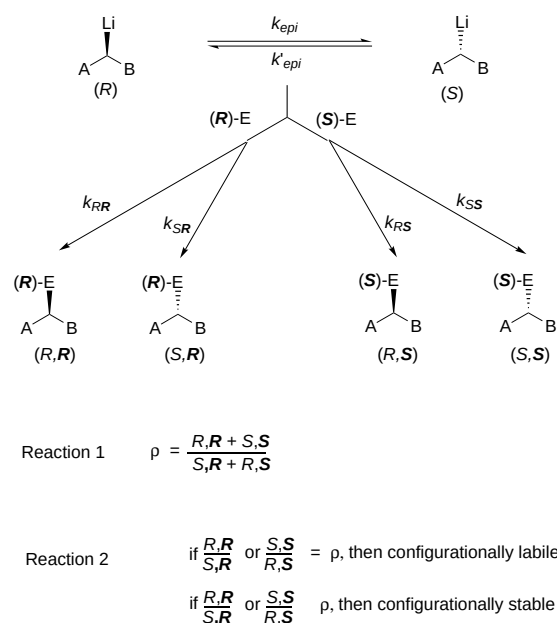
The effect of an intermolecular chelating ligand on the barrier of inversion of an α -seleno organolithium compound has been investigated.^[23] The $\Delta G^\ddagger_{\text{inv}}$ for **24** was found to be 12.1 kcal mol⁻¹, both in the absence or presence of diamine **25**, which is consistent with C–Se bond rotation as the rate-determining step (Scheme 13).

Scheme 13. α -Lithioselenide **24** is also configurationally labile in the presence of chelating diamine **25**.

In summary, the use of NMR spectroscopy as a probe for configurational behavior has provided a wealth of mechanistic information about the inversion process. The technique has broad scope and utility because of the ability to use achiral or racemic organolithium reagents. This technique has led to the identification of three types of mechanisms for inversion: a) a classical dissociative mechanism that involves the separation of the lithium atom from the organolithium carbon atom, followed by configurational inversion and recombination; b) a mechanism in which the dissociation process is facilitated by inter- or intramolecular Lewis base coordination; c) a final mechanism which does not involve dissociation in the rate-determining step—in this case, a bond rotation provides the highest energy barrier, usually as a result of some steric or stereoelectronic interaction. Thus, although several details of the inversion process have been clarified, it is clear that no single factor dominates the configurational behavior of organolithium species studied to date.

2.2. Determination of Configurational Stability Based on Kinetic Resolution (Hoffmann Test)

For our understanding of the mechanism and rates of inversion to be synthetically meaningful, this knowledge needs to be related to the rate of the reaction of the organolithium compound with an electrophile. Thus, an appreciation of configurational stability during an electrophilic substitution step can be of great value when developing synthetic methods that require chiral organolithium reagents. With this aim in mind, Hoffmann and co-workers have developed a chemical test of configurational stability based on kinetic resolution during the electrophilic substitution step.^[24–26] The Hoffmann test consists of the two reactions, as outlined in Scheme 14. In the first reaction, which is a control reaction, the racemic organolithium compound is allowed to react with a racemic mixture of a chiral electrophile. It is desirable that the diastereomeric ratio of the resulting products lies between 1.5 and 3.0. In the second reaction, the racemic organolithium compound is treated with enantiopure electrophile. If the diastereomeric ratio of the products is the same as that obtained with the racemic electrophile, the organolithium is configurationally labile with respect to the rate of reaction with that particular electrophile. However, if the ratio of products from the second reaction differs from that observed in the control reaction, the organolithium is at least partially configurationally stable. In the case of an organolithium compound that is completely configurationally stable on the time scale of the reaction, the diastereomeric ratio from the second reaction should be equal to one. Although, in principle, any electrophile that meets the Hoffmann test criteria can



Scheme 14. Outline of the Hoffmann test for the determination of configurational stability. Reaction 1 is carried out with a racemic electrophile (E). Reaction 2 is carried out with an enantioenriched electrophile. If ρ for Reaction 1 is between 1.5 and 3.0, the electrophile is suitable for the Hoffmann test.

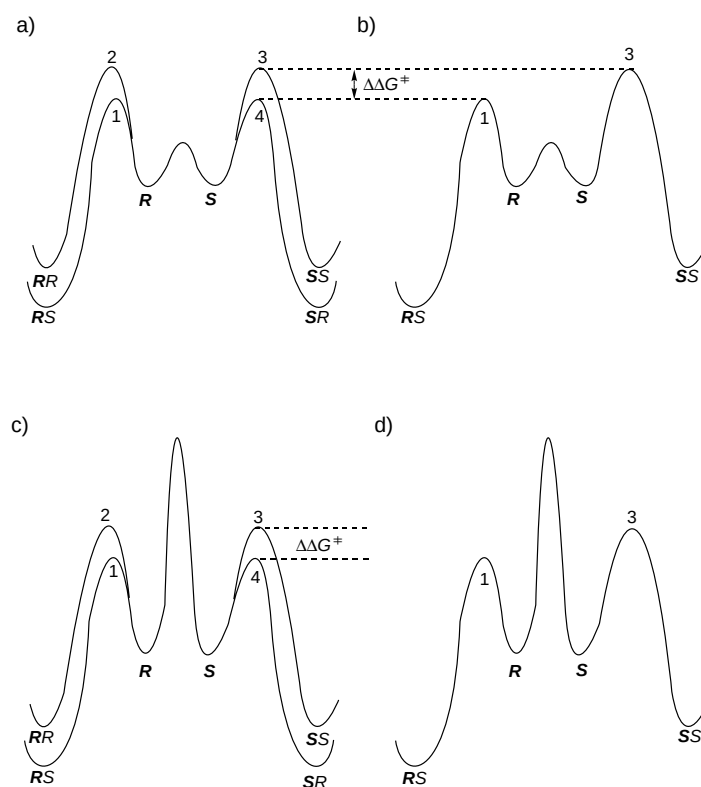


Figure 1. Energy diagram of the reaction kinetics of the Hoffmann test: a) and b) Reactions of a configurationally labile intermediate with the racemic electrophile or the pure *S* enantiomer. The product ratios are dependent on $\Delta\Delta G^\ddagger$; c) and d) Reactions of a configurationally stable intermediate with the racemic electrophile or the pure *S* enantiomer. The product ratios in c) are dependent on $\Delta\Delta G^\ddagger$, whereas d) shows that the product ratio is independent of $\Delta\Delta G^\ddagger$ in limiting cases.

be used, the vast majority of the reactions to date have involved the use of the Reetz aldehyde, *N,N*-dibenzylalaninal.^[27]

The kinetic basis for the Hoffmann test can be understood by considering the energy diagrams in Figure 1. Figures 1a and 1b represent the reactions of a configurationally labile intermediate with the racemic and with the *S* enantiomer of an electrophile, respectively. In the reaction with the racemic electrophile, four different pathways are available for the equilibrating racemic organolithium intermediates. Since pathways 1 and 2 are enantiomeric to pathways 4 and 3, the overall diastereoselectivity of the product is determined by the diastereomeric transition state energy difference $\Delta\Delta G^\ddagger$ (Figure 1a). In the reaction with only the *S* enantiomer of the electrophile, trajectories 1 and 3 are the only pathways available for the equilibrating organolithium intermediate. However, since equilibration of the enantiomers is faster than the reaction with the electrophile, the overall diastereoselectivity of this reaction will still be determined by the diastereomeric transition state energy difference $\Delta\Delta G^\ddagger$ (Figure 1b). Thus, the diastereoselectivity of the reaction of a configurationally labile organolithium intermediate should be the same, regardless of whether the electrophile is racemic or enantiomerically pure. This situation represents a classic Curtin–Hammett situation.^[28]

Figures 1c and 1d represent the reaction of a configurationally stable intermediate with the racemic and with the *S*

enantiomer of the electrophile, respectively. In the reaction with the racemic electrophile, pathways 1 and 2 are available for the *R* enantiomer of the organolithium intermediate, whereas pathways 3 and 4 are available for the *S* enantiomer of the organolithium intermediate. As before, pathways 1 and 2 are enantiomeric to pathways 4 and 3, respectively, and the overall diastereoselectivity of the product is still determined by the energy difference $\Delta\Delta G^\ddagger$ of the transitions states of the diastereomers.

However, the results of the reaction with an enantioenriched electrophile would differ for configurationally stable and configurationally labile intermediates. For configurationally stable intermediates, in the reaction with only the *S* enantiomer of the electrophile, the only available pathway for the *R* enantiomer of the organolithium compound is pathway 1 and the only available pathway for the *S* enantiomer of the organolithium compound is pathway 3. Since the intermediates are not at equilibrium, the diastereomeric ratio of the products will reflect the ground-state enantiomeric ratio of the organolithium intermediate, provided that the reaction is allowed to go to completion. Therefore, in the ideal case of a racemic configurationally stable organolithium intermediate, the diastereoselectivity of the products from the reaction represented by Figure 1d would be equal to one.

It is critical that the reaction with the enantioenriched electrophile proceeds with high conversion; excess electrophile is usually used. Furthermore, if the intrinsic diastereoselectivity of the reaction is excessively large, the amount of “mismatched” reaction product from pathways 2 and 3 may be too small to be detected. The fact that racemic organolithium species can be used, as well as the requirement for low intrinsic diastereoselectivity allows one to conduct the Hoffmann test even with organolithium reagents and/or electrophiles that do not exhibit synthetically useful stereoselectivities. Furthermore, since the ratio obtained from the control reaction is the kinetic ratio, it can also be obtained by using the enantioenriched electrophile at very low conversions or by using it in substoichiometric amounts.

A modification of the Hoffmann test allows one to probe the rates of interconversion of organolithium species that are complexed to a chiral ligand.^[29] Complexation renders the two interconverting species diastereomeric instead of enantiomeric, thereby disrupting the energy symmetry of the configurational inversion process. In this case, two experiments that are very similar to the original Hoffmann test, are conducted, except that only enantioenriched electrophile is used. The reactions are carried out by using stoichiometric and substoichiometric amounts of this electrophile. If the product stereoisomer ratios are different in the two cases, then the organolithium compound is configurationally stable on the timescale of the experiment. However, with diastereomeric organolithium complexes, the observation of identical product ratios does not necessarily imply configurational lability, and further experiments are required. Figure 2 shows an energy diagram for a case in which diastereomeric complexes (or diastereomers, as the test can be applied to both) do not rapidly interconvert relative to the rate of their reaction with the electrophile. The reaction with a stoichiometric amount of electrophile reflects the starting ratio of complexes *R*·L and

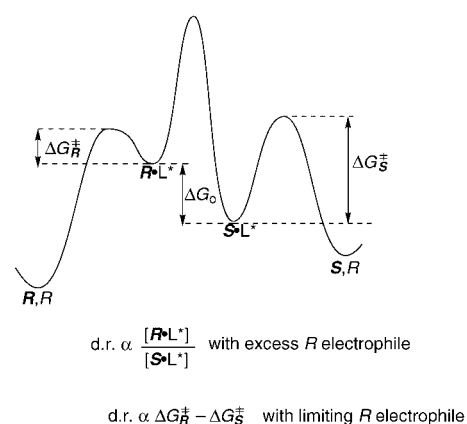


Figure 2. Kinetics of the modified Hoffmann test with non-equilibrating diastereomeric complexes. In the case of excess *R* enantiomer of the electrophile, the product ratio is dependent on the concentration ratio of the complex. When the *R* enantiomer is the limiting reagent, the product ratio is dependent on the difference in the activation enthalpies.

S·L. If the system is allowed to reach thermodynamic equilibrium, the product ratio reflects the ground-state energy difference ΔG_0 . Once again, it is important to ensure that the reaction proceeds to completion; excess electrophile is generally used. In the reaction with small amounts of electrophile (very low conversion), the product ratio will reflect the differences between the activation energies, $\Delta G_S^\ddagger - \Delta G_R^\ddagger$, corrected for the relative population of the diastereomeric intermediates. At higher conversions, the ratio will of course shift towards the value obtained in the first reaction.

Identical ratios of stereoisomeric products in the two reactions can arise from two possible scenarios: a) the system is configurationally labile, and the product ratios in both reactions are the result of a dynamic kinetic resolution (Figure 3); b) the system is configurationally stable, but the activation energies for electrophilic substitution are identical ($\Delta G_S^\ddagger = \Delta G_R^\ddagger$). In the first case, the product ratio for both reactions will be determined by $\Delta\Delta G^\ddagger$. To distinguish between the two cases, one needs to be able to determine the starting ratio of diastereomeric complexes. If this ratio is not the same as the product ratio, then the system is configurationally labile. However, if the ratios are the same, then no kinetic resolution has occurred, and the configurational behavior cannot be determined—different electrophiles or reaction conditions must be tried.

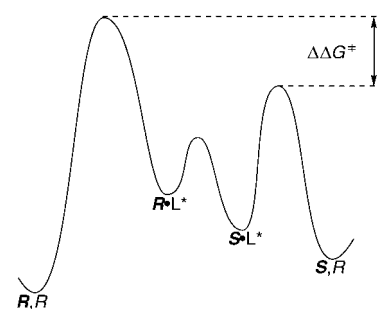


Figure 3. Kinetics of the modified Hoffmann test with rapidly equilibrating diastereomeric complexes. The product ratio is dependent on the activation enthalpies, both when the *R* enantiomer is in excess or when it is the limiting reagent.

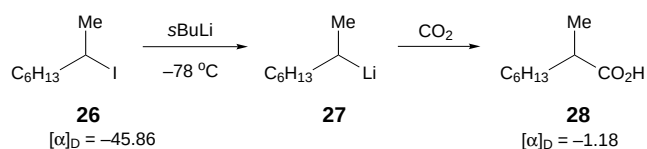
The Hoffmann test for diastereomeric complexes has been modified further to enable the use of achiral electrophiles.^[30–32] The transition states that result from these complexes are diastereomeric as a result of the chiral ligand, and thus the electrophile no longer requires a stereocenter. In the modified test, the products are enantiomeric instead of diastereomeric, and the enantiomer ratio is determined instead of the diastereomer ratio.

The Hoffmann test and its variations have been applied to a wide variety of organolithium reagents. Although the successful interpretation of the results from a Hoffmann test does not require knowledge of the stereochemical course of the electrophilic substitution step in reactions of enantiomeric organolithium compounds, this is not the case with diastereomeric intermediates. Regardless of the actual invertive/retentive partition during electrophilic substitution of a given enantiomer of an organolithium compound, the other enantiomer must, by necessity, react with the same partition ratio because the pathways are isoenergetic. However, the stereochemical course of electrophilic substitution for two diastereomeric intermediates, which can differ in energy, need not be identical. While Ockhams's razor has led to the assumption of the more simple theory (identical stereochemical behavior for both diastereomers), this is an issue that may need to be examined more carefully in some cases.

3. Chiral Organolithium Reagents

3.1. Nonheteroatom α -Substituted Organolithium Compounds

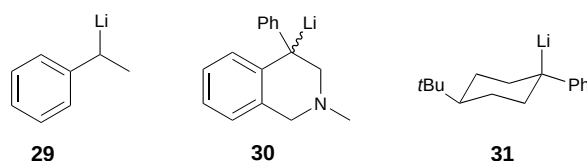
To the best of our knowledge, the first enantiomerically enriched organolithium compound was reported by Letsinger in 1950, who prepared the organolithium intermediate **27** by treating (–)-2-iodooctane (**26**) with *sec*-butyllithium (*s*BuLi) at -70°C in a petroleum ether/diethyl ether mixture.^[33] The organolithium intermediate retained approximately 20% of its original configuration to provide optically active (–)-2-methyloctanoic acid (**28**) after treatment with CO_2 (Scheme 15). Higher reaction temperatures or use of polar solvents afforded the product with diminished optical activity, presumably as a result of racemization of the organolithium intermediate.^[34]



Scheme 15. The first enantioenriched organolithium compound **27**, which was used in the synthesis of optically active (–)-2-methyloctanoic acid (**28**).

Nozaki et al. reported that deprotonation of ethylbenzene with *n*BuLi/(–)-sparteine followed by electrophilic substitution provided enantioenriched products, albeit with poor selectivities.^[35] The resulting benzyllithium compound **29** was subsequently established to be configurationally labile under

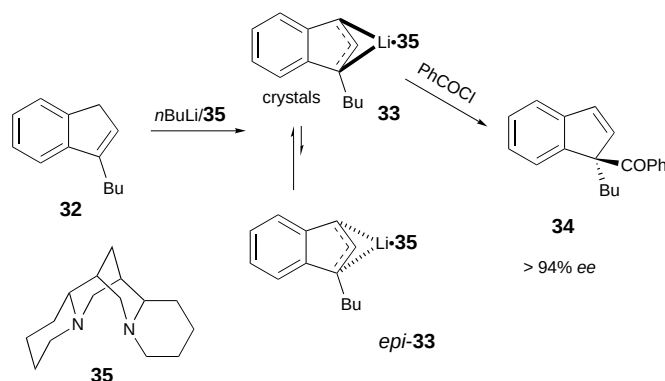
the conditions of the Hoffmann test.^[36] The related benzyllithium intermediate **30** also undergoes electrophilic substitution under dynamic resolution, but it is not known whether it is under kinetic or thermodynamic conditions (Scheme 16).^[37]



Scheme 16. Earlier benzyllithium intermediates used in the first studies of configurational stability.

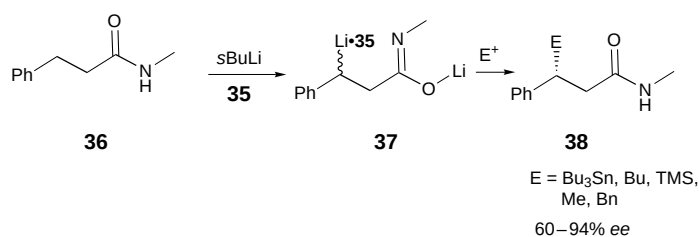
In contrast, protonation of benzyllithium compound **31** with deuterated water or dihydronaphthalene provides products with different *cis/trans* ratios in each case.^[38] This result is taken to indicate that epimerization of **31** is competitive with the rate of protonation. Alternatively, the different diastereomeric ratios could arise from different amounts of retentive and invertive protonation.

A single enantiomer of a benzyllithium compound can be selectively stabilized by crystallization in a chiral environment.^[39] Treatment of 1-butylnaphthalene (**32**) with a mixture of *n*BuLi and (–)-sparteine (**35**) provided the organolithium intermediate **33** as a single crystalline diastereomer. Treatment of **33** with benzoyl chloride occurred with retention of configuration to afford **34** (*ee* > 94%; Scheme 17).

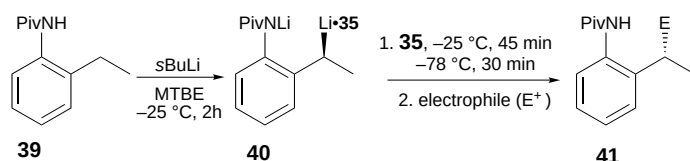
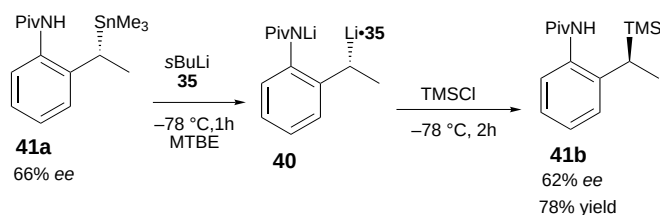


Scheme 17. Stereoselective crystallization/substitution of **33** in the presence of (–)-sparteine (**35**).

The (–)-sparteine-mediated substitution of enantiomeric β -lithiated amides has been reported. Treatment of secondary amide **36** with *s*BuLi/**35** afforded the organolithium intermediate **37**, which reacted with electrophiles to afford the substituted products **38** with good to excellent enantiomeric excesses (Scheme 18).^[40] The configurational stability of the organolithium intermediate in the absence of diamine was established by using Sn/Li exchange experiments.^[40, 41] However, in the presence of (–)-sparteine, the intermediate **37** exhibits a rate of epimerization that is comparable with that of the electrophilic substitution with trimethylsilyl chloride (TMSCl) at -78°C , as determined by means of a modified Hoffmann test. At -100°C the rate of epimerization is sufficiently slow to result in a dynamic thermodynamic resolution.^[41]

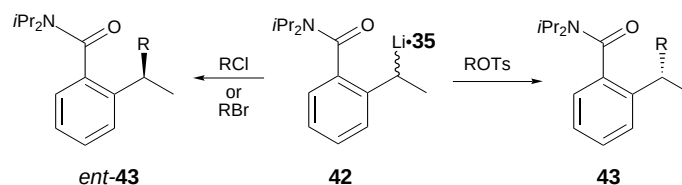
Scheme 18. (–)-Sparteine-mediated dynamic resolution of **37**.

Stereoselective (–)-sparteine-mediated lateral lithiation reactions of *N*-pivaloyl aniline **39** and *o*-ethyl-*N,N*-diisopropylbenzamide have been carried out.^[42–44] In the case of the lithiated aniline **40**, highly enantioenriched products were obtained by allowing the diastereomeric organolithium intermediate to reach thermodynamic equilibrium at -25°C . Subsequent cooling to -78°C followed by electrophilic substitution provided products with high enantiomeric ratios (Scheme 19). Intermediate **40** was shown to be configurationally stable in the presence of *N,N'*-dibutylbispidine, an achiral (–)-sparteine mimic. Lithio-destannylation of the enantioenriched organostannane **41a** at -78°C in the presence of (–)-sparteine followed by reaction with electrophiles provided an enantiomeric series of products (Scheme 20). The Sn/Li exchange is presumed to proceed with retention of configuration, followed by invertive electrophilic substitution.

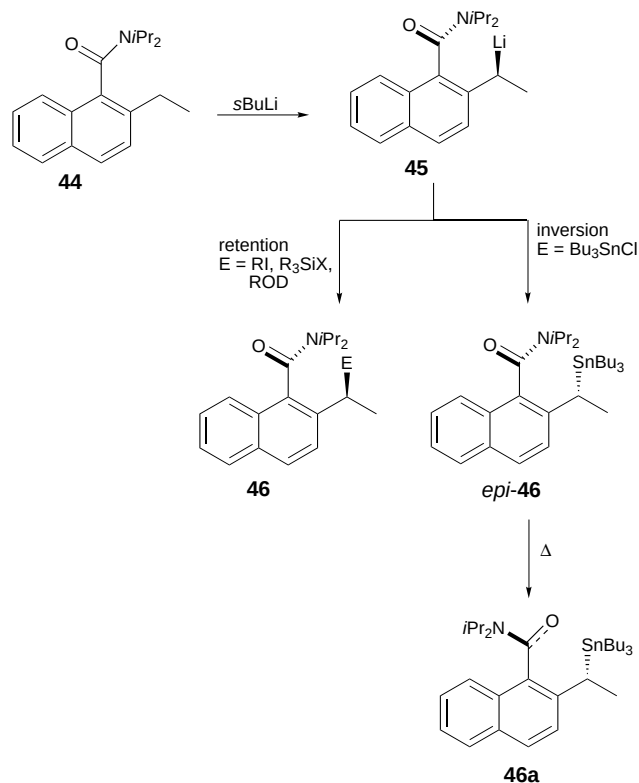
Scheme 19. Enantioselective (–)-sparteine-mediated lithiation/substitution of **39**.Scheme 20. Stereoconversion in the lithiation/substitution of stannane **41a**.

In contrast, lithiated benzamide **42** is configurationally labile at -78°C . A modified Hoffmann test was carried out with allyl tosylate as the electrophile, and provided results consistent with a dynamic kinetic resolution pathway. Remarkably, the reaction of the organolithium compound with alkyl halides provided products with absolute configurations opposite to those of the products obtained from the reaction with alkyl tosylates (Scheme 21). It was suggested that retentive electrophilic substitution is favored by the slower reacting tosylates, thus allowing the sulfonyl oxygen atom to coordinate to the lithium cation.^[43] Highly reactive electrophiles such as triflates, and electrophiles without Lewis basic

sulfonyl oxygen atoms such as alkyl halides are proposed to react through an invertive transition state without precoordination to the lithium atom.

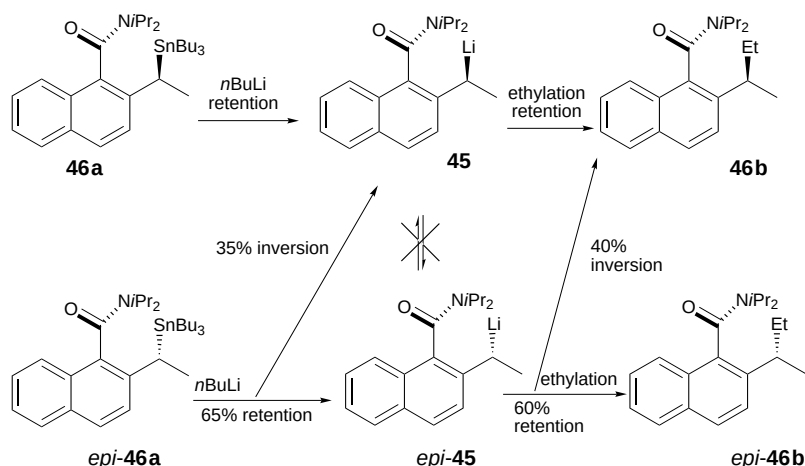
Scheme 21. Lithiation of the side chain and stereodivergent substitution of **42**.

A related diisopropyl naphthamide **44** undergoes highly atroposelective reactions to provide benzylic substitution products **46** with high diastereoselectivities.^[45–48] Lateral lithiation of the naphthamide occurs stereoselectively to provide a single diastereomeric intermediate, presumed to be the *syn* diastereomer **45**.^[49] This intermediate undergoes reaction with alkyl and silyl halides and methanol with retention of configuration, but stannylation occurs with inversion (Scheme 22). The *anti* stannane *epi*-**46** can be epimerized to **46** upon prolonged heating. The lithiated intermediates are configurationally stable at -40°C .^[47]

Scheme 22. Atroposelective lithiation/substitution at the side chain of **44**.

The lithiated naphthamide exhibits unique stereochemical behavior in its electrophilic substitution. The thermodynamically favored *syn* atropisomer **45** can be formed readily either by deprotonation of **44** or by Sn/Li exchange of the *syn*

stannane **46a**. The epimeric organolithium compound *epi*-**45** is formed by lithio-destannylation of the *anti* stannane *epi*-**46a**. The *anti* organolithium compound *epi*-**45** is also configurationally stable, and retains its configuration even after two hours at -40°C . The Sn/Li exchange of *epi*-**46a** also proceeds partially with inversion, since both diastereomeric organolithium species were detected by means of NMR spectroscopy. However, the final product ratio after ethylation does not correspond to the organolithium ratio observed in the NMR spectra, thus indicating a lack of stereoselectivity in the electrophilic substitution of the *anti* organolithium. It is proposed that the inversion occurs during the actual lithio-destannylation step, but alternative mechanisms such as the formation of different “ate” complexes may also be operative (Scheme 23).^[50, 51]

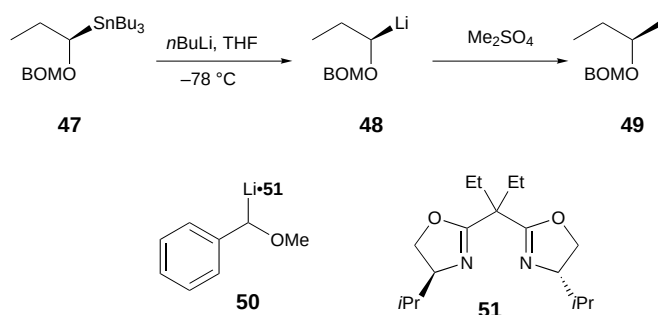


Scheme 23. Stereodivergent lithio-destannylation and substitution of **46a**.

3.2. α -Alkoxy-Substituted Organolithium Compounds

3.2.1. Nondipole-Stabilized Compounds

Organolithium intermediates with α -alkoxy substituents have attracted considerable interest since Still and Sreekumar's seminal report in 1980.^[52] In that work, they reported the preparation of the enantioenriched α -benzyloxymethyl (BOM) organolithium compound **48** through lithio-destannylation of the enantioenriched tributyltin-substituted precursor **47**. Alkylation of the organolithium with dimethyl sulfate afforded BOM-protected (*R*)-2-butanol **49** with overall retention of configuration at the carbanion center and no detectable racemization. The configuration of **48** was maintained at temperatures as high as -30°C (Scheme 24). This methodology has been expanded by improved procedures for the preparation of enantioenriched α -alkoxy stannanes.^[53, 54] Similarly, application of the modified Hoffmann test to the benzylic organolithium intermediate **50** established its configurational stability in the presence of the bisoxazoline ligand **51**.^[55, 56]



Scheme 24. Enantioselective lithiation/substitution of α -oxyorganolithium compounds **48** and **50** (BOM = benzyloxymethyl).

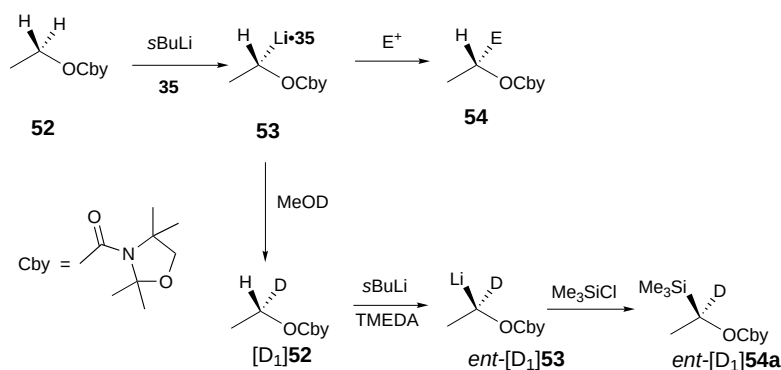
3.2.2. Dipole-Stabilized Compounds

The protection of an alcohol as a hindered carbamate activates the α -carbon atom towards lithiation as a result of dipole stabilization as well as of the directing-group ability of the carbamate moiety. These umpolung synthons provide a powerful method for the synthesis of chiral alcohols. Hoppe and co-workers have extensively developed the lithiation/substitution reaction sequence in the presence of (–)-sparteine to prepare enantioenriched alkyl carbamates. This work has been reviewed recently.^[1]

Carbamates such as **52**, which are derived from primary alcohols, undergo enantioselective deprotonation by alkylolithium compounds in the presence of (–)-sparteine to provide configurationally stable organolithium intermediates (Scheme 25). A large kinetic isotope

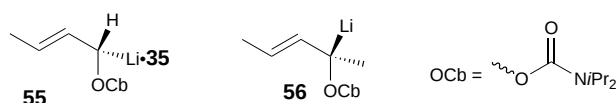
effect was measured for the deprotonation step, and the lithiated intermediates react with electrophiles with retention of configuration in most instances. These two features have been elegantly combined by employing deuterium as a “protecting group”; both enantiomers of a product were obtained from a single enantiomer of the chiral ligand.^[57, 58]

Modification of the substrate structure has a significant effect on the behavior of the organolithium intermediate. In the case of the secondary crotyllithium, selective crystalliza-



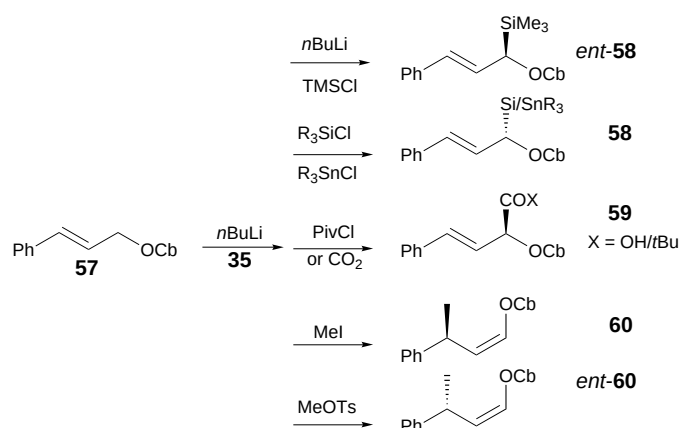
Scheme 25. (–)-Sparteine-mediated enantioselective deprotonation of carbamates derived from primary alcohols.

tion of a single diastereomer provided **55**, which reacts with $(\text{OiPr})_4\text{Ti}$ with inversion of configuration.^[59–62] The related tertiary crotyl intermediate **56** was configurationally stable and underwent substitution with either retention or inversion, depending on the electrophile (Scheme 26).^[63, 64]



Scheme 26. Configurationally stable allylic α -oxyorganolithium reagents.

The stereo- and regioselectivity of the cinnamyl intermediate **57** depends on the nature of the electrophile (Scheme 27). When the deprotonation was carried out in the presence of TMSCl , (*R*)-**58** was isolated with 58% *ee*. Similarly, when



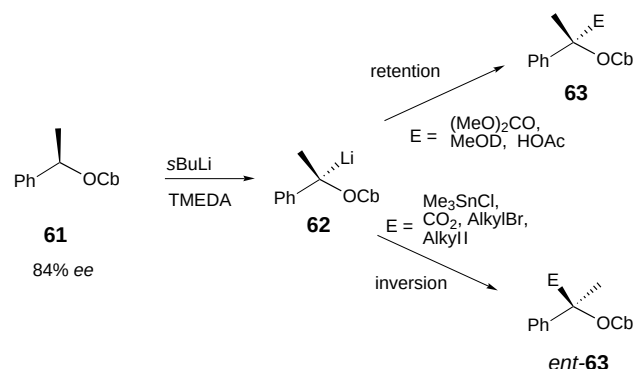
Scheme 27. Regio- and stereodivergent lithiation/substitution of cinnamyl intermediate **57**.

methyl iodide was added to the organolithium solution six minutes after deprotonation, the γ -substituted product **60** was obtained with 34% *ee*, whereas methylation after thirty minutes or at any time thereafter resulted in an *ee* value of 50%. These results suggest that the diastereomeric complex which is formed upon deprotonation epimerizes within thirty minutes in a thermodynamic ratio. A modified Hoffmann test with methyl iodide as the electrophile confirmed that a dynamic thermodynamic resolution was operative, and that the minor diastereomer reacted faster.

Previous studies of the deprotonation of alkyl carbamates with $n\text{BuLi}/(-)\text{-sparteine}$ have established a strong preference for the abstraction of the pro-*S* proton followed by electrophilic substitution with retention of configuration.^[65] Thus, deprotonation of **57** is presumed to initially generate an *S*-configured organolithium compound, which epimerizes over time to the *R* complex, unless TMSCl is present. In this scenario, silylation must occur with inversion of configuration. Reaction with methyl iodide also occurs with inversion in an *anti-S_{E'}* fashion, whereas methyl tosylate reacts via a *syn-S_{E'}* transition structure.

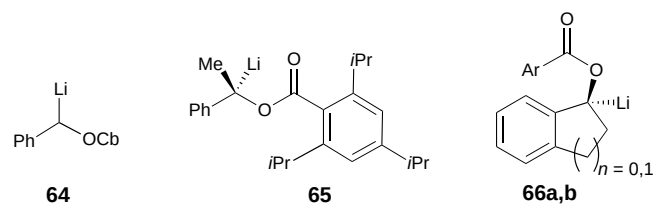
Tertiary lithium intermediates derived from benzyl carbamates also undergo electrophile-dependent stereodivergent substitution.^[66–68] Carbamate **61**, which is derived from (*R*)-1-

phenylethanol, was deprotonated with $s\text{BuLi}/\text{TMEDA}$ at -78°C . The reaction of intermediate **62** with acetic acid, [*D*]methanol, or dimethyl carbonate occurred with retention of configuration, whereas reaction with carbon dioxide or alkyl halides provided products with inversion of configuration (Scheme 28). These results indicate that the organolithium **62** is configurationally stable under the reaction conditions. The invertive substitution of Me_3SnCl can be exploited to access either enantiomer of the products.^[69] A Hoffmann test on the related secondary organolithium compound **64** (Scheme 29) indicated that it was configurationally stable on the time scale of reaction with the Reetz aldehyde.^[70]



Scheme 28. Stereodivergent electrophilic substitution of configurationally stable tertiary benzyllithium compound **62**.

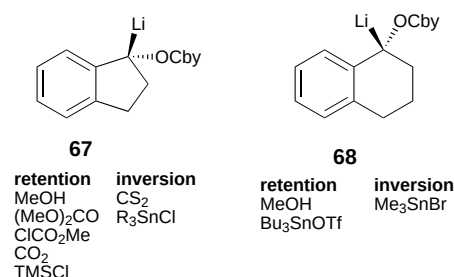
Hammerschmidt and Hanninger observed identical behavior with **65**, which has a triisopropylbenzoate instead of a carbamate as the directing group.^[71] The absolute configuration of the stannylated intermediate was determined by means of crystallographic analysis, and indicated that stannylation does, in fact, occur with inversion of configuration.^[69] This principle was further extended to cyclic benzyl lithium intermediates **66a,b**, which are derived from tetralol and indanol (Scheme 29).^[72] The related carbamate derivatives **67** and **68** exhibit increased configurational stability relative to



Scheme 29. Benzylic α -oxyorganolithium reagents.

their ester counterparts.^[72, 73] Again, the reaction between the diisopropyl carbamate and electrophiles in general occurs with retention of configuration, whereas trimethyltin bromide provides the product of invertive substitution. Notably, reaction with tributyltin triflate occurs with retention of configuration (Scheme 30).

Lithiated α -alkoxy species, particularly dipole-stabilized intermediates, are amongst the most widely used organo-



Scheme 30. Stereodivergent electrophilic substitution of carbamate derivatives **67** and **68**.

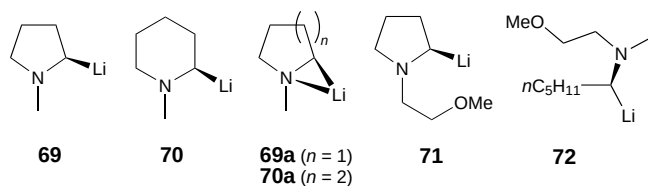
lithium reagents. Thus, it is not surprising that considerable effort has been devoted to the development of asymmetric reactions with these reagents. The preparation of configurationally stable α -alkoxy species, initially by Sn/Li exchange of enantioenriched stannanes and later by (–)-sparteine-mediated deprotonation of alkyl carbamates, are both general and powerful methodologies. Even intermediates with little or no configurational stability, such as allyl and benzyllithium compounds, undergo highly selective reactions, often through dynamic resolution pathways.

3.3. α -Amino-Substituted Organolithium Compounds

Chiral α -amino carbanions are of great synthetic value owing to their use in the stereoselective syntheses of natural and non-natural amino acids and alkaloid natural products.^[74–76] α -Amino organolithium compounds are most frequently generated by Sn/Li exchange, following Peterson's method for the preparation of dialkylaminomethylolithium.^[77, 78] However, the formation of many secondary organolithium compounds through this route can be problematic. Thus, there is little information about the configurational stability of chiral acyclic α -amino organolithium compounds that are not dipole-stabilized or chelated.^[79–82]

3.3.1. Nondipole-Stabilized Compounds

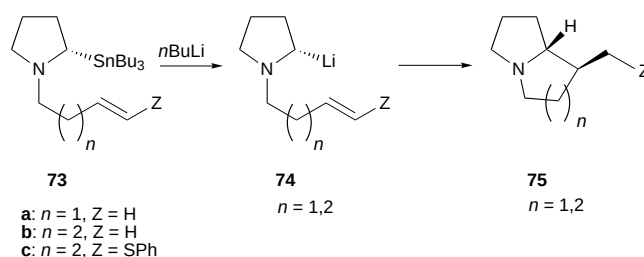
The cyclic nonstabilized 2-lithio-*N*-methylpyrrolidine (**69**) and 2-lithio-*N*-methylpiperidine (**70**) were generated from the corresponding enantioenriched organostannanes.^[83] Both **69** and **70** are configurationally stable for at least 45 min at -40°C , but significant decrease in the enantiopurity was observed at -20°C . It was also observed that **71**, which has a potential internal coordination site, is configurationally less stable than **69**, although **71** is more stable than the acyclic analogue **72** (Scheme 31). The increased stability of **69** is



Scheme 31. α -Lithioamines examined for configurational stability.

attributed to structure **69a**. Recent NMR spectroscopic studies have shown that **69** exists as a dimer in solution, whereas **70** remains monomeric. The existence of the bridged structure **69a** was confirmed by the observation of ^{15}N – ^6Li coupling in the NMR spectra.^[11] Whereas a conformationally locked structure in **69a** increases the barrier to racemization, the presence of a coordinating methoxy group in **71** facilitates epimerization, presumably through a conducted-tour mechanism.^[84] Acceleration of epimerization as a result of the coordinating ability of the pendant group has been observed with several dipole-stabilized organolithium intermediates. The reactions of **69** and **70** with alkyl halides occur with inversion of configuration, whereas retention is observed in reactions with carbonyl electrophiles.^[85]

The configurational stability of acyclic α -amino organolithium reagents that can be stabilized by chelation have been reported.^[81] The enantioenriched organolithium intermediate **72** is configurationally stable at -95°C in THF. However, higher temperatures or the presence of chelating solvents such as dimethoxyethane resulted in a significant decrease in enantiopurity. The influence of the rate of electrophilic substitution on the rate of configurational inversion is highlighted by the anionic cyclization shown in Scheme 32. Lithio-destannylation of the enantioenriched organostannane **73a** (94% *ee*) followed by cyclization provided the [5,5] ring system **75a** in high yield and with complete retention of

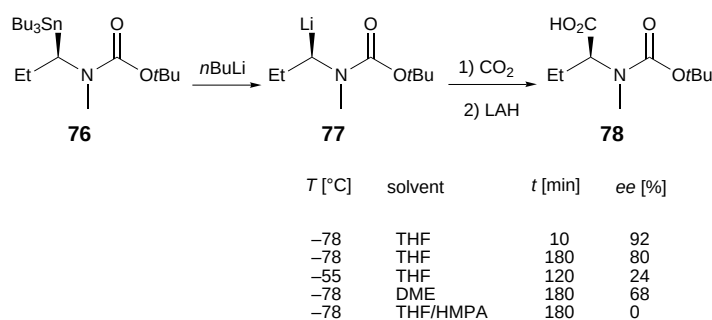


Scheme 32. Stereoselective cyclization of a chiral α -lithioamine.

configuration.^[86] In contrast, cyclization of the organolithium onto the pentenyl side chain ($n = 2$) provided the product with poor stereoselectivity.^[87] The rate of cyclization to form the six-membered ring was approximately sixteen times slower than that for the five-membered ring formation, thus slowing down the substitution step enough for it to be competitive with the rate of racemization. Introduction of an anion-stabilizing thiophenyl group (e.g. **73c**) increased the rate of cyclization and afforded the bicyclic product with good stereoselectivity (72% *ee*).^[87]

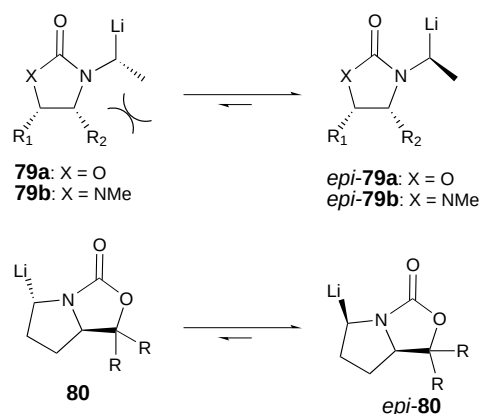
3.3.2. Dipole-Stabilized Compounds

The dipole stabilization of the lithiated intermediate has a significant effect on the configurational stability. Sn/Li exchange of **76** affords the organolithium intermediate **77**, which is moderately configurationally stable at -78°C .^[88] Higher temperatures or the presence of coordinating solvents such as dimethoxyethane or HMPA decreases the configurational stability (Scheme 33).



Scheme 33. Configurational stability of the acyclic dipole-stabilized α -lithioamine **77**.

Studies of related diastereomeric species have also provided evidence for configurational stability of dipole-stabilized intermediates.^[80, 89] The lithiated oxazolidinones **79a/b** and **80** rapidly epimerize at -78°C to diastereomers which are more configurationally stable (Scheme 34). The faster epimerization of the carbamate was ascribed to the poorer coordinating ability of a carbamate oxygen atom relative to the urea oxygen atom. This indicates that the dissociation of the lithium ion from the heteroatom is important for inversion.^[79, 80] The organolithium intermediates were prepared by Sn/Li exchange of the appropriate organostannane precursors.

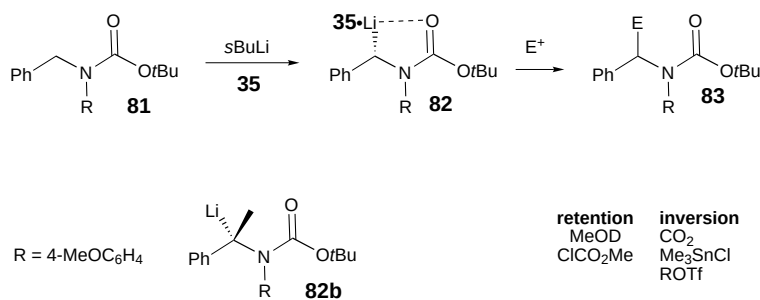


Scheme 34. Epimerization of diastereomeric α -lithioamines.

The benzylic organolithium intermediate **82** is configurationally stable in the presence of (–)-sparteine, but it is labile in the presence of TMEDA or in the absence of any chelating diamine.^[90, 91] The (–)-sparteine/intermediate complex was characterized by means of NMR spectroscopy and found to be monomeric, with the lithium ion complexed to both the carbamate and (–)-sparteine.^[90] A modified Hoffmann test with methyl triflate as the electrophile identified the major diastereomeric complex as marginally more reactive towards methylation. The intermediate **82** reacts with acyl halides with retention of configuration, whereas inversion is observed in the reactions with alkyl triflates (Scheme 35). Stannyl chlorides react with inversion and Sn/Li exchange occurs with retention of configuration, thus this methodology allows access to both enantiomers of the products. The correspond-

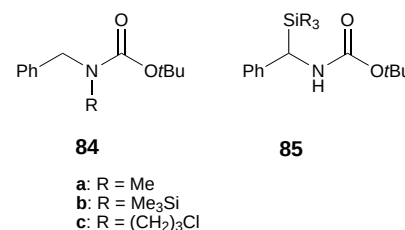
ing tertiary organolithium **82b** is configurationally stable in the presence of TMEDA, and also undergoes stereodivergent electrophilic substitution, as observed with **82**.

The lithiation/substitution of the related **84a** proceeds through an asymmetric deprotonation, followed by racemization and diastereoselective precipitation of a single (–)-sparteine complex.^[92] The lithiated intermediate was configurationally labile in the presence of TMEDA, but the configurational stability in the presence of (–)-sparteine was not determined. In contrast, the intramolecular cyclization reaction of **84c** proceeds through an asymmetric deprotonation pathway, as illustrated by Sn/Li exchange and isotope



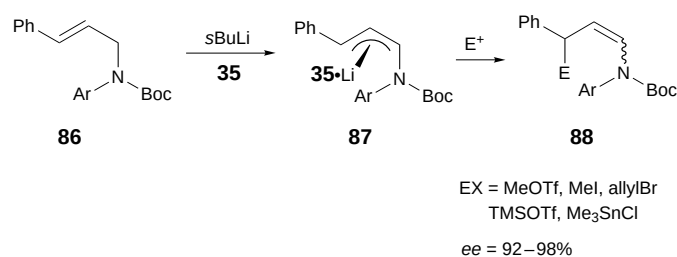
Scheme 35. Stereodivergent (–)-sparteine mediated lithiation/substitution of **82**.

effect experiments.^[93] Lithiation of the related *N*-silyl-*N*-Boc-benzylamine **84b** (Boc = *tert*-butoxycarbonyl) with *n*BuLi/(–)-sparteine is followed by anionic rearrangement to provide benzylic silane **85** with moderate enantioselectivities (Scheme 36).^[94]



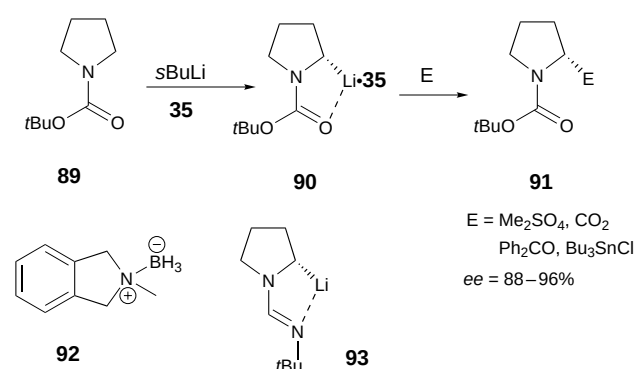
Scheme 36. Benzylamine derivatives **84** and **85**, which undergo stereoselective lithiation/substitution.

Beak and co-workers have reported the lithiation/substitution of cinnamylamine derivative **86**.^[31, 95, 96] Treatment of **86** with *n*BuLi in the presence of (–)-sparteine followed by electrophilic substitution provided products **88** with high *ee* values (Scheme 37). The major organolithium intermediate was identified to be *endo-syn-anti-87* by means of both NMR spectroscopic and solid-state studies.^[97] Under the standard reaction conditions of lithiation at -78°C followed by electrophilic substitution at the same temperature, the major pathway involved asymmetric deprotonation to provide a configurationally stable intermediate. However, when the reaction sequence was conducted at -25°C , both dynamic kinetic and dynamic thermodynamic resolution pathways were operative.^[31] Both enantiomers of the products are accessible by invertive substitution reactions of the enantiomeric organolithium intermediate or by a retentive Sn/Li exchange of the enantioenriched organostannane.



Scheme 37. Enantioselective lithiation/substitution of cinnamylamine derivative **86**.

The lithiation of *N*-Boc-pyrrolidine (**89**) in the presence of (–)-sparteine followed by electrophilic substitution affords 2-substituted pyrrolidines **91** with high *ee* values.^[98, 99] Results from deuterium substitution and Sn/Li exchange experiments showed that the formation of the configurationally stable intermediate **90** was the critical step in the determination of the stereochemistry. The enantioselective deprotonation and substitution of the related isoindoline–borane complex **92** has also been reported (Scheme 38).^[100] The configurational



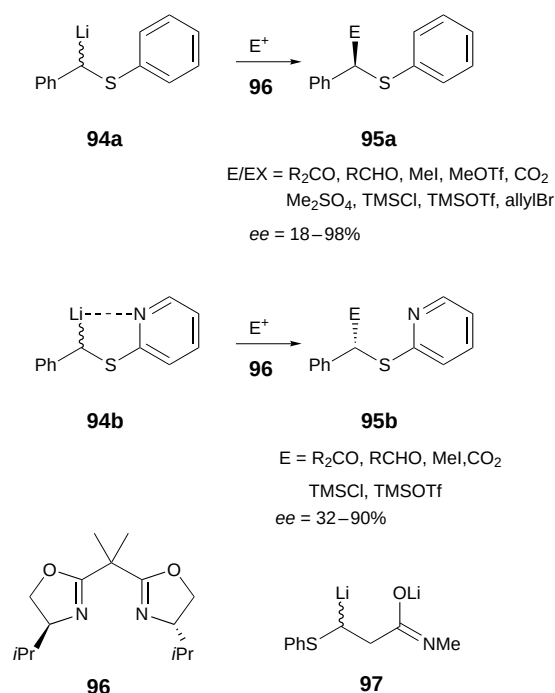
Scheme 38. Enantioselective lithiation/substitution of pyrrolidine derivatives.

stability of **90** and related organolithium intermediates depends on the nature of the dipole-stabilizing group and its geometry. Meyers and Elworthy have compared the configurational stability of **90** with the formamidinium derivative **93** and found the latter to be more configurationally stable.^[101] The difference was attributed to the better coordinating ability of the oxygen atom relative to the nitrogen atom, thus facilitating a concerted-tour pathway for inversion.

3.4. Sulfur-Containing Compounds

α -Lithio sulfides have been studied extensively because of the utility of lithiated dithianes as acyl anion equivalents. Studies of α -lithio sulfides have revealed novel mechanisms for configurational inversion which can be attributed to the $n-\sigma^*$ interaction with the sulfur atom. Many diastereoselective reactions of α -lithio sulfides have been reported and reviewed.^[102, 103] Highly enantioselective lithiation/substitution sequences of α -lithio sulfides are known. The benzylic α -thio organolithium compound **94** undergoes enantioselective

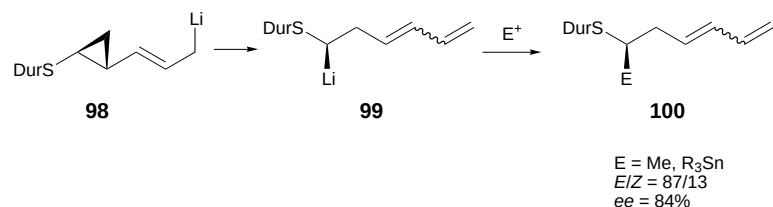
lithiation/substitution in the presence of the bisoxazoline **96**.^[104, 105] A Hoffmann test indicated that the organolithium was configurationally labile both in the presence and absence of TMEDA.^[70] The configurational lability of **94a** in the presence of the chiral ligand was studied with a modified Hoffmann test.^[104] The reaction of **94a** with both 0.2 equivalents as well as with excess benzophenone provided the product with an *ee* value of 92% in both cases, which suggests the operation of a dynamic kinetic resolution. Consistent with this hypothesis, the enantiomeric ratios of the products were found to be highly dependent on the electrophile (Scheme 39). However, very different results were observed when the same reaction sequence was carried out with the pyridyl analogue **94b**.^[105] The absolute configurations of the thiopyridyl substitution products were opposite to those of the thiophenyl products. Furthermore, the highest enantiomeric ratios were obtained after a “warm-cool” sequence, thus suggesting a dynamic thermodynamic resolution as the reaction pathway which was confirmed by using a modified Hoffmann test.



Scheme 39. Enantioselective substitution of α -lithiophenyl and pyridyl sulfides **94a**, **94b**, and **97**.

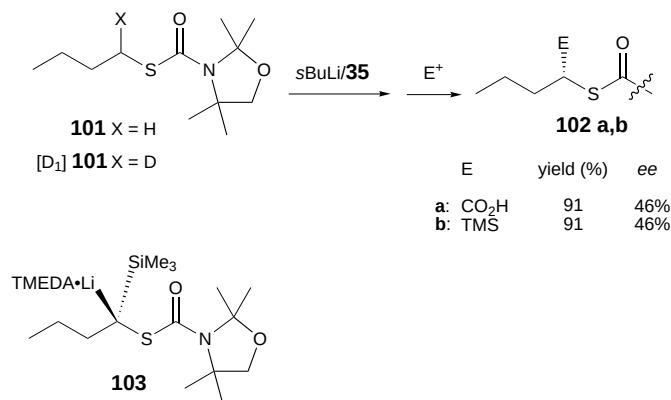
Based on molecular modeling, the authors proposed a retentive electrophilic substitution for **94a** and an invertive process for **94b**. Simultaneous coordination of the lithium cation by both the pyridyl nitrogen atom and the chelating ligand is believed to block the front face of **94b**. In contrast, the back face of carbanion **94a** is hindered as a result of the *anti* orientation of the thiophenyl group relative to the C–Li bond which is necessary for maximizing $n-\sigma^*$ overlap. Enantioenriched α -lithio sulfides have also been generated by a retrocarbolithiation of a cyclopropyl group.^[106] The lithiated intermediate **99** can be trapped with methyl iodide or stannylating agents to provide products **100** with retention of

configuration (Scheme 40, Dur = 2,3,5,6-tetramethylphenyl). The ring opening occurs with retention of configuration to provide a lithiated intermediate, which is configurationally stable at -105°C but racemizes at -78°C (half-life = 90 min). This corresponds to an inversion barrier of $13.3\text{ kcal mol}^{-1}$, similar to that measured for other lithiated duryl sulfides.^[21]



Scheme 40. Cyclopropane ring-opening to provide a configurationally stable α -thio organolithium compound.

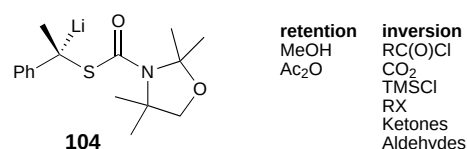
The enantioselective lithiation/substitution of thiocarbamate **101** provides products with a moderate enantiomeric excess.^[107] Treatment of **101** with *s*BuLi/**35** followed by reaction with carbon dioxide or TMSCl provided **102a** or **102b** in excellent yields and moderate enantioselectivities. Treatment of $[\text{D}_1]\text{101}$ with TMSCl under the same reaction conditions provided $[\text{D}_1]\text{102b}$ with complete retention of deuteration and an *ee* value of 34 %, which indicates that the deprotonation is not stereoselective. The configurational behavior of the secondary lithiated intermediate is unknown. The related tertiary lithiated carbamate **103** is configurationally stable at -78°C (Scheme 41).^[108]



Scheme 41. Enantioselective lithiation/substitution of α -thiocarbamates.

The tertiary benzylic organolithium **104**, generated by deprotonation of the enantioenriched thiocarbamate, is configurationally stable at -78°C , and even at 0°C for up to ten minutes.^[108] The reactions of the organolithium compound with methanol and acid anhydrides occur with retention of configuration, whereas acyl chlorides, aldehydes, ketones, alkylating agents, carbon dioxide, and TMSCl all provide the products of invertive substitution (Scheme 42).^[109]

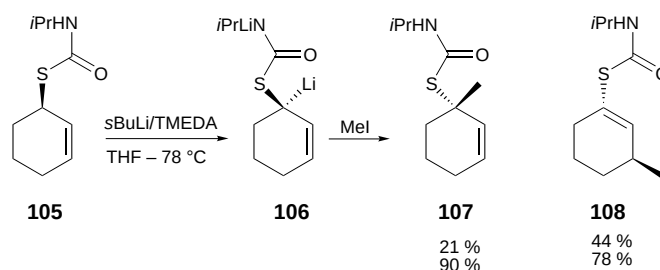
The allylic dilithio intermediate **106**, obtained by deprotonation of the enantioenriched precursor **105**, exhibits interesting solvent-dependent configurational stability.^[110] Race-



Scheme 42. Stereodivergent substitution of configurationally stable lithiated thiocarbamate **104**.

mization occurs readily at -78°C in diethyl ether and toluene, but the organolithium compound is stable for 4.5 hours in THF at the same temperature. Methylation is not completely regioselective, and affords both α - and γ -substitution products derived from invertive and *anti*- S_{E} alkylation, respectively. Rotation about the C–S bond is believed to be the rate-determining step. By analogy to other α -lithio sulfides, which have been studied in detail by means of NMR spectroscopy,

the configurational stability is highest under conditions that favor increased ion-pair formation (Scheme 43).



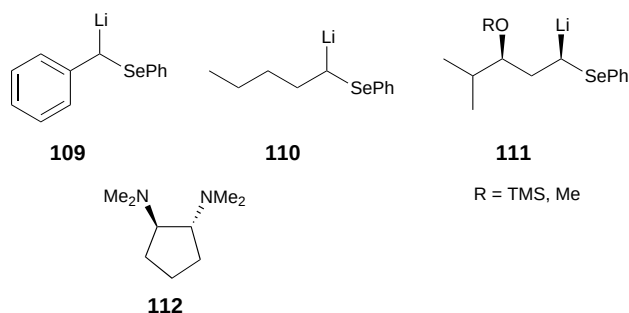
Scheme 43. Lithiation/substitution of chiral allylic thiocarbonate **105**.

Despite the extensive use of diastereomeric α -thio organolithium reagents as probes for studying configurational stability and inversion, until recently there have been very few synthetic applications of enantioenriched α -lithio sulfides. Chiral ligand mediated lithiation/substitution of α -lithio thioethers and thiocarbamates have illustrated the potential for carrying out stereoselective transformations with these reagents, and further developments and applications of chiral α -lithio sulfides can be expected.

3.5. Selenium-Containing Compounds

The configurational stability of chiral acyclic selenides have been studied by using the Hoffmann test, with varying results.^[9, 25] Benzyl lithium compound **109** inverts faster than it reacts with aldehydes at -78°C in THF, but allyllithium **110** is configurationally stable in a mixture of THF and diethyl ether at -105°C . Organolithium compound **111** rapidly isomerizes to diastereomers (9:1) at -78°C , but epimerization is competitive with the rate of electrophilic substitution at lower temperatures (-100°C) (Scheme 44).^[111]

Although organolithium compound **24** (Scheme 13) is configurationally labile, the presence of chiral diamine ligand **112** favors the formation of diastereomeric complexes (9:1) that react with electrophiles at a faster rate than they undergo

Scheme 44. α -Lithioselenides studied for configurational stability.

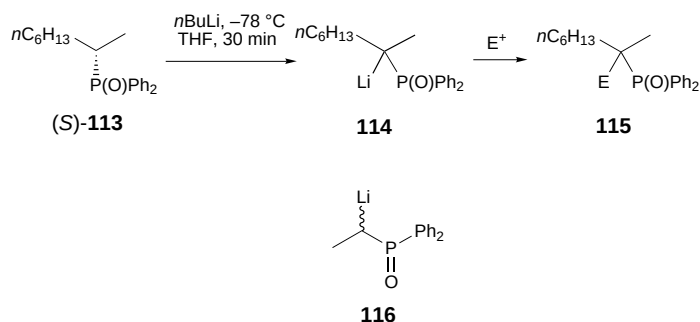
inversion. Competition experiments showed that uncomplexed **24** reacted faster with electrophiles than either of the diastereomeric complexes.^[112] However, complexation of **24** with cyclohexyldiamine **25** afforded diastereomeric complexes (7:3) that reacted with electrophiles faster than the uncomplexed organolithium compound. These results indicate that an external ligand can be used to modulate the reactivity of organolithium compounds.

3.6. Phosphorus-Containing Compounds

Phosphorus-stabilized organolithium compounds are of interest owing to their potential application in the stereoselective preparation of alkenes and in other aspects of asymmetric synthesis.^[113, 114] Structural and mechanistic investigations indicate that the lithium ion in most α -lithiophosphonates, α -lithiophosphonamides, and α -lithiothiophosphonamides are not in contact with the carbon atom.^[115–119] There are only a few examples in which such carbon–lithium contacts were observed by means of NMR spectroscopy or X-ray crystallography.^[120, 121] In general, these carbanions are nearly planar and are considered to be formally sp^2 hybridized at the carbon center.^[118, 122]

O'Brien and Warren have studied the configurational stability of enantioenriched phosphane oxides. Treatment of (*S*)-**113** (95% *ee*) with *n*BuLi or lithiumdiisopropylamide (LDA) followed by reaction with electrophiles afforded the product **115** as a racemic mixture, even when trimethylsilyl chloride was used as an internal electrophile.^[123] The Hoffmann test was carried out with the secondary organolithium **116** and the Reetz aldehyde as the electrophile, and the lithiated intermediate was found to be configurationally labile under the reaction conditions (Scheme 45).^[124]

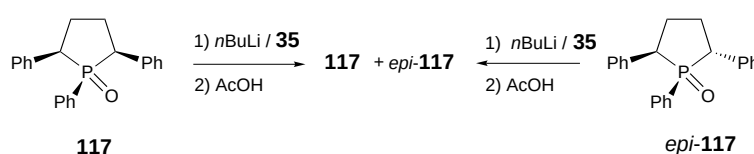
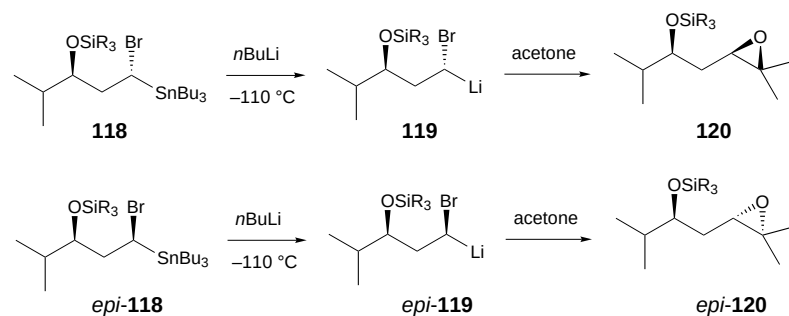
The α -lithio derivative of 1,2,5-triphenylphospholane **117** is configurationally stable in the presence of (–)-sparteine.^[125] Treatment of **117** with *n*BuLi/(–)-sparteine followed by reaction with acetic acid afforded the products **117** and *epi*-**117** (1:2, 45% *ee* for the latter). When *epi*-**117** was used as the starting material for the reaction, the products were obtained in >99:1 ratio, and the product *epi*-**117** was racemic. The different product stereoselectivities from **117** and *epi*-**117** indicate that the organo-

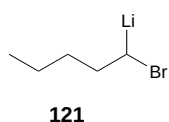
Scheme 45. Configurationally labile enantiomeric α -lithio phosphane oxides.

lithium intermediate is not configurationally labile.^[126] The diastereoselectivity of the reaction and the facial selectivity of electrophilic substitution was dependent on the protonating agent (Scheme 46).

3.7. Halogen-Containing Compounds

α -Halo organolithium reagents, which are useful intermediates for the synthesis of epoxides and cyclopropanes, are usually prepared by Li/Sn or Li/halogen exchange.^[127–131] The epimeric intermediates **119** and *epi*-**119** were generated by the former route and provided diastereomeric epoxides upon reaction with acetone, thus demonstrating useful configurational stability under the reaction conditions (Scheme 47).^[132] These conclusions were consistent with the results of a modified Hoffmann test.^[133] Dibromide precursors also undergo diastereoselective Li/halogen exchange to provide stereoisomerically enriched intermediates. Enantiomeric α -halolithium reagents have not been as extensively studied. A Hoffmann test was conducted on racemic α -bromoalkyllithium **121** generated by Li/halogen exchange of the dibromide.^[25] The organolithium **121** underwent addition to the Reetz aldehyde faster than it underwent configurational inversion, thus demonstrating functionally useful configura-

Scheme 46. After lithiation of **117** and *epi*-**117** and treatment of the resulting phosphane oxide with acetic acid, a mixture of epimers was obtained.Scheme 47. Configurationally stable diastereomeric α -halo organolithium compounds.



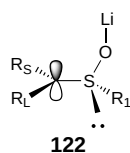
Scheme 48. Chiral α -bromo organolithium studied by means of the Hoffmann test.

tional stability at -110°C which could make α -haloorganolithium compounds important intermediates in stereoselective synthesis (Scheme 48).

4. Stereochemistry of Electrophilic Substitution

The preceding material illustrates the diverse organolithium structures that undergo highly stereoselective lithiation/substitution reactions. The lithiated intermediates range widely in their configurational stabilities, but it is also clear that configurational stability is not a prerequisite for highly stereoselective substitution reactions, since highly enantioenriched products can also be obtained by means of dynamic kinetic resolutions. However, the frequency of invertive and stereodivergent electrophilic substitution, both in configurationally labile and configurationally stable organolithium compounds, is noteworthy.

Electrophile-dependent stereochemistry in electrophilic substitution has been observed with a variety of diastereomeric organolithium intermediates, especially lithiated sulfoxides.^[134] α -Lithio sulfoxides exhibit a propensity to undergo electrophilic substitution to provide products in which the incoming electrophile is *syn* to the sulfoxide oxygen atom when the incoming reagent has an electrofugal group that can coordinate to the lithium atom. Addition of lithium salts or other Lewis acids often perturbs this selectivity, presumably by altering the coordination environment of either the organolithium compound or of the electrofuge.^[135–138] Crystallographic and spectroscopic studies indicate that α -lithio sulfoxides are best represented by structure **122**.^[103] Electro-



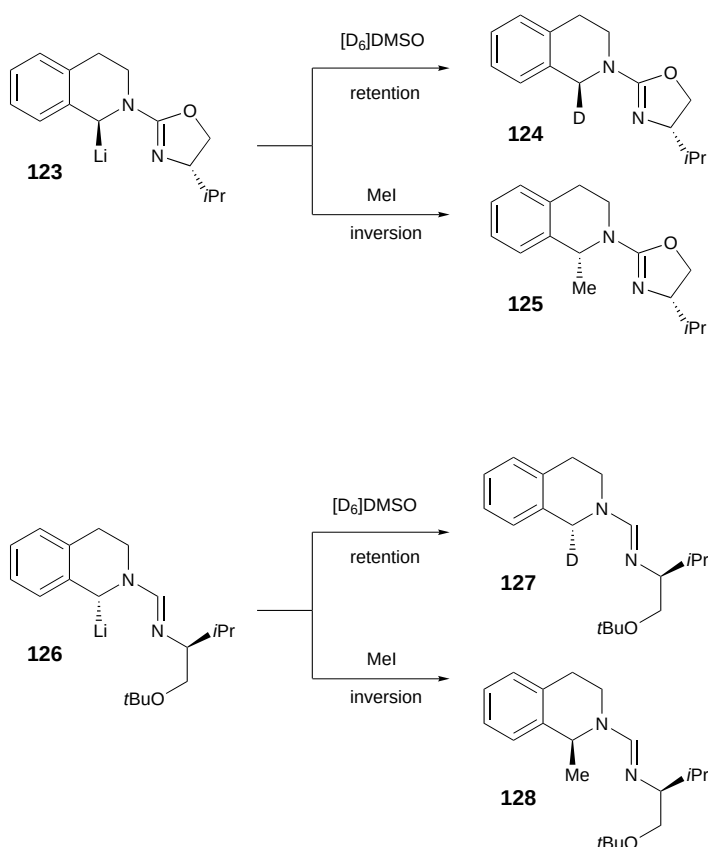
Scheme 49. Planar α -lithio sulfoxides permit stereodivergent electrophilic substitution.

fugal groups that can coordinate to the lithium atom are believed to deliver the electrophile to the top face, whereas all other species react from the bottom face. Large R^1 groups increase the steric hindrance towards bottom face alkylation, and a decrease in stereoselectivity is observed (Scheme 49).

The coordination of a lithium atom to a sulfoxide has also been invoked to rationalize the stereochemistry of deuteration reactions with $[\text{D}_6]\text{DMSO}$. In the alkyla-

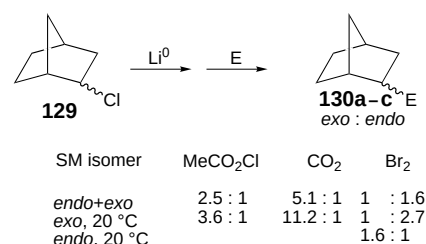
tions of α -lithio tetrahydroisoquinoline derivatives **123** and **126**, Meyers/Dickman and Gawley independently found that deuteration with $[\text{D}_6]\text{DMSO}$ gave the opposite stereochemistry to that observed in the alkylation with methyl iodide (Scheme 50).^[139, 140] Retentive deuteration was proposed to occur through the coordination of the sulfoxide oxygen atom to the lithium cation. The configurations of **123** and **126** were inferred from other experiments directed at addressing the selectivity of the deprotonation.

Stereodivergence based on the electrophile was first identified in the late 1960s in the earliest studies of chiral organolithium reagents.^[141, 142] A series of experiments demonstrated that the stereochemistry of the lithiation/substitution of norbornyl chloride (**129**) was dependent on the choice



Scheme 50. Diastereodivergent substitution of lithiated tetrahydroisoquinolines.

of electrophile.^[141] Substitution of 2-norbornyllithium afforded products with electrophile-dependent *exo/endo* ratios. These ratios were independent of the stereochemistry of **129**. When the organolithium compound was generated from the *exo* chloride at 20°C instead of at 36°C , the selectivities were higher. Remarkably, the reaction of bromine with the organolithium compound derived from the *endo* chloride at 20°C provided *exo* bromide **130c** as the major product (Scheme 51). If a predominantly retentive Li/halogen exchange at 20°C is assumed, these results are consistent with a



Scheme 51. Diastereodivergent substitution of norbornyllithium.

pathway that involves retentive electrophilic substitution of carbon dioxide and methyl chloroformate and invertive substitution of bromine. Although the configurational stability of the norbornyllithium was not independently examined, the observation that the product ratio is dependent on the

temperature of organolithium formation suggests that complete equilibration does not occur at 20 °C or below.

Despite these early results, the retentive pathway remained the paradigm for electrophilic substitution of organolithium reagents until fairly recently. In large part this is a result of the historical scarcity of organolithium reagents whose absolute configurations were known; hence the stereochemical course of the electrophilic substitution could not be determined. Thus, in the absence of experimental evidence suggesting otherwise, retentive substitution remained the simplest explanation consistent with the facts. Electrophilic substitution of allylic carbamates **56** and **55** (Scheme 26) provided examples of invertive processes, but since there is substantial precedent for *anti*-S_E processes, these results are not extraordinary. However, the electrophile-dependent stereodivergent substitution of benzyllithium **62** (Scheme 28) provided a clear example of an anomalous pathway, and one which was not restricted to an allylic system.

Table 3 highlights the diversity of organolithium reagents for which enough information about the configuration of the lithiated intermediate is known such that a reasonable hypothesis about the steric course of the substitution step can be made. Entries 2,3,7–9,11, and 17 are tertiary organolithium compounds which are generated by deprotonation of an enantioenriched precursor, and their configuration is assigned by assuming a retentive deprotonation. The configuration of the structures in entries 5 and 6 have been assigned on the basis of X-ray crystallography. The configuration of the remaining organolithium compounds shown in the table are not unequivocally established, but are reasonable hypotheses based on additional mechanistic information available in each case. With a few exceptions, a large number of the cases involve benzyl, allyl, or cinnamyl organolithium reagents which are capable of delocalizing the negative charge over several atoms. Although such intermediates are usually distorted from an ideal tetrahedral geometry, the X-ray crystal structures of **55** (Scheme 26) and **87** (Scheme 37) indicate that the carbanion center retains a small degree of pyramidalization and is not completely planar.^[61, 97] Planarization serves to reduce the steric difference between the front and back faces of the carbanion, although the presence of an external ligand perturbs that symmetry.

Beyond this simple correlation, few prominent trends emerge. Of the organolithium reagents that undergo invertive or stereodivergent substitution, reactions with alkyl and trialkyltin halides always provide products of invertive substitution. Notably, in the lone case where tributyltin triflate was used as an electrophile (Table 3, entry 9), the reaction occurred with retention of configuration, which suggests that stannylation may also be subject to nucleofuge-dependent electrophilic substitution.^[72] However, despite these anomalous results, stannylation reactions of most configurationally defined organolithium reagents occur with retention of configuration. The α -lithio pyrrolidine and piperidine derivatives (Table 3, entry 1) are not delocalized organolithium compounds, and Gawley et al. has suggested that invertive electrophilic substitution is actually the “default” pathway for the reactions of **69** and **70** (Scheme 31).^[143] Alkyl halides react through this “standard” invertive pathway, whereas electro-

philes that are capable of coordinating to the lithium atom, provide products with retention of configuration. In this case, retentive substitution with alkylating agents is believed to become a competitive pathway only when unfavorable steric interactions interfere with the invertive process.

A variety of explanations have been put forward to rationalize the stereochemical course of the electrophilic substitution step. It has been suggested that HOMO/LUMO interactions control the partitioning between retentive and invertive substitutions in the case of benzylic organolithium compound **62** (Table 3, entry 8; Scheme 28).^[67] It was proposed that the increased planarization of **62** increases electron density on the rear face of the C–Li bond, thus increasing the probability for an approaching electrophile to interact with the back face. A similar explanation has been put forward for the invertive substitution of the pyridyl sulfide **94b** (Scheme 39).^[105] Electrophiles that have a low-energy LUMO react rapidly with the carbanion through an invertive pathway. Electrophiles that are not very Lewis basic and cannot coordinate to the lithium atom are also suggested to undergo the invertive substitution. Electrophiles that can coordinate effectively to the lithium atom or have a higher energy LUMO and react slowly with the organolithium compound undergo retentive substitution. Similar rationalizations have been proposed for the substitution of the α -amino benzyllithium **82** (Table 3, entries 10 and 11; Scheme 35) and benzamide **42** (Table 3, entry 13; Scheme 21).^[43, 90]

There have been a few attempts to study this issue by using theoretical techniques. The structure of CH₃Li₂⁺ was calculated by using ab initio methods, which indicated that the D_{3h} isomer **132** was favored over the C_s structure **133** by 2.5 kcal mol^{–1} (Scheme 52).^[146] The authors of the study noted that the D_{3h} structure is a potential model for invertive electrophilic substitution, as well as an intermediate in an intra-aggregate configurational inversion process that involves lithium atom exchange. Computational methods have been used to study the stereochemical pathways for the electrophilic substitution of the indanyl and benzylic organolithium compounds **134** and **135**.^[73] The ground-state structures of the lithiated intermediates were calculated and optimized by using semiempirical methods. The sum of bond angles at the lithiated carbon atom of **135** was calculated to be 333.1°, consistent with partial planarization of the carbanion, although far from the 360° expected for an ideal planar structure. In contrast, the sum of angles of **134** was 323.8°, representative of increased puckering of the tetrahedral center (Scheme 53). Calculated energies for the completely planar organolithium compounds, which are possible transition states for an invertive substitution, indicated that the barrier to planarization for **134** was 4.1 kcal mol^{–1} higher than that for **135**. Although these results provide a rationale for why the benzyllithium compound undergoes invertive substitution more readily than the indanyl species, they do not account for the intrinsic preference for invertive over retentive substitution.

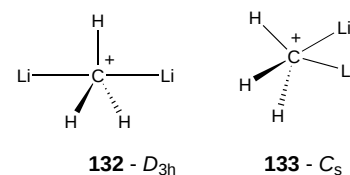
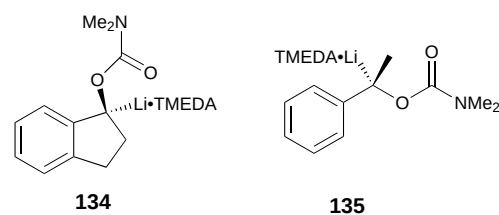
Qualitatively, these are all reasonable explanations, but they are nevertheless retroactive rationalizations. A model that can reliably predict the stereochemical course of an electrophilic substitution has yet to be formulated. For

Table 3. Configurationally defined organolithium intermediates that undergo stereodivergent substitution.

Entry	Lithiated Intermediate	Electrophiles which react with retention	Electrophiles which react with inversion	Ref
1		CO ₂ , ClCO ₂ Me, (MeO) ₂ CO, RCHO, R ¹ COR ²	RX (X = Cl, Br, I)	[85, 143]
2		Ti(OiPr) ₄	TiCl(NEt ₂) ₃ , Me ₃ SnCl	[144]
3		Ti(OiPr) ₄ , CO ₂ , ClCO ₂ Me, Bu ₃ SnCl		[144]
4		MeOTs (δ)	TMSCl, R ₃ SnCl, PivCl, CO ₂ , MeI (δ)	[32]
5			Ti(OiPr) ₄ , CO ₂ , R ₃ SnCl	[63]
6		MeOD, Michael acceptors (δ), R ¹ COR ² , ClCO ₂ Me	Me ₃ SnCl, (α und δ), TMSOTf, CO ₂ , R-X, (X = Cl, Br, I)	[31]
7			MeI	[110]
8		MeOH, R ¹ COR ² , RCHO, (MeO) ₂ CO	HOAc, Me ₃ SnCl, RNCO, RCOCl, CO ₂ , R-X, (X = Cl, Br, I), CS ₂ , ClCO ₂ Me	[66, 67]
9		MeOH, (MeO) ₂ CO, Bu ₃ SnOTf, ClCO ₂ Me	Me ₃ SnBr, Bu ₃ SnCl, Bu ₃ SnBr, CS ₂	[73]
10		MeOH, ClCO ₂ Me	Me ₃ SnCl, CO ₂ , ROTf	[90]
11		MeOH, ClCO ₂ Me	Me ₃ SnCl, CO ₂ , ROTf	[90]
12		MeOH	ZnBr ₂	[145]

Table 3. (Continued)

Entry	Lithiated Intermediate	Electrophiles which react with retention	Electrophiles which react with inversion	Ref
13		ROTs	RX	[43]
14			RCHO, ROTs, RX, Me ₃ SnCl, R ¹ COR ²	[43]
15		R ¹ COR ² , CO ₂ , MeI, TMSCl, TMSOTf		[105]
16		RX, TMSX, MeOD	Bu ₃ SnCl	[47]
17		MeOH, (RCO) ₂ O	RCOCl, CO ₂ , TMSCl, R-X, RCHO, R ¹ COR ²	[108, 109]

Scheme 52. Two calculated structures for CH₃Li₂⁺, which represent retentive (**133-C_s**) and invertive (**133-D_{3h}**) electrophilic substitution.

Scheme 53. Calculated structures of planar benzylic organolithium intermediates.

example, the electrophile methyl chloroformate reacts with inversion as well as with retention of configuration, depending on the particular organolithium compound (Table 3, entries 8 and 9). One of the biggest challenges towards understanding the nature of electrophilic substitution derives from the scarcity of structural information on the organolithium reagents. Only two of the organolithium species in Table 3 (entries 5 and 6) have been characterized structurally by means of X-ray crystallography.^[61, 97] Both crystallize as monomers bound to the bulky (–)-sparteine ligand, which effectively blocks the *syn* face of the organolithium compound. However, structures such as **69** and **70** (Table 3,

entry 1; Scheme 31), which undergo stereodivergent substitution in the absence of any ligands, are likely to exist as more aggregated complex structures.^[143]

These aggregation states of the organolithium compound may influence the stereochemical course of the reaction. A D_{3h} -like arrangement of lithium atoms with an Li-C-Li angle of 168° has been observed crystallographically in the solid-state structure of benzylolithium, thus suggesting that either face of the organolithium compound can undergo electrophilic substitution readily.^[147] Thus, although a reaction may appear invertive in a unimolecular context, it may very well be that aggregation positions lithium atoms on both faces of the carbanion, thereby providing a four-centered transition state for both invertive and retentive substitutions. However, the extended angle observed in the benzylolithium is the exception rather than the rule, and most crystallographically observed Li-C-Li angles are significantly smaller. What is clear at this stage is that the stereochemical course of the electrophilic substitution of an organolithium compound cannot be generally assumed to occur through a retentive process. But, to be forewarned is to be forearmed, and it is imperative that each case be examined carefully. As additional examples are discovered and more structural information becomes available, we shall undoubtedly develop a better understanding of the factors that dictate the stereochemical pathway of electrophilic substitution.

5. Summary and Outlook

The important role of organolithium reagents in various synthetic transformations continues to provide the impetus for studies of the mechanisms of stereoselective reactions of organolithium compounds with a variety of physical organic tools. For example, NMR spectroscopy has provided information on the thermodynamic parameters involved in the inversion process and the solution structures of key organolithium intermediates. In many instances, factors that facilitate the dissociation of the lithium ion from the carbanion center, such as polar solvents, additives, or internal Lewis bases, are found to enhance the rate of epimerization. However, neither the dissociation of the lithium ion nor the configurational inversion is always the rate-determining step, particularly in the case of α -lithio sulfides and some dipole-stabilized carbanions.

Further data were derived from chemical reactivity and other mechanistic experiments. Hoffmann's test based on kinetic resolution has been an invaluable tool since it does not require inherently high stereoselectivities in reactions to obtain information on configurational stability. The test provides information about the relative rates of epimerization and substitution. Sn/Li exchange and deuterium labeling experiments provide information about the configurational stability as well as mechanism of formation of the chiral organolithium intermediate, and they complement the information afforded by the Hoffmann test. These experiments also provide information about the organolithium intermediate prior to the addition of an electrophile, and therefore represent the configurational stability on the timescale of standard reaction conditions, that is, the time the organo-

lithium spends in the reaction mixture during the lithiation step. The configurational stability depends on solvent, temperature, the nature of the neighboring heteroatom, intra- or intermolecular coordination of Lewis bases, and whether or not the anion is conjugated with a π system.

Another important step in lithiation/substitution sequences is the facial selectivity of the approach of the electrophile during substitution. Electrophile-dependent retentive or invertive substitutions have now been observed for many cases. With a few exceptions, the carbanion in these cases is conjugated with a π system. There have been much speculation on the reasons for the observed trend. However, the lack of structural information has restricted opportunities for systematically expanding the scope of such reactions. Only in very few cases do we have a clear structure/function relationship for the stereochemical behavior of organolithium compounds. The solvent plays an important role in the configurational stability, often by providing a Lewis base site for lithium coordination, but it also affects the aggregation state of the organolithium compound. The connection between aggregation state and chemical behavior has not been as thoroughly studied with organolithium reagents as it has with lithium amides, and recently, lithiated alkynes. Substantial advances have been made in correlating the solution structures of these intermediates with their chemical behavior.^[148–150]

What are the future opportunities and challenges in this field? We believe that the first of these challenges is the development of a systematic structure–function relationship for the stereochemical behavior of organolithium compounds. There have only been a few instances in which structural information about organolithium aggregates have been used as the starting point for the design of stereoselective lithiation/substitution sequences.^[151, 152] A second and more challenging goal is the development of catalytic processes that use organolithium reagents. Ligand-catalyzed methodologies for the addition of organolithium reagents to imines have been reported.^[153, 154] However, this has not been extended to other lithiation/substitution sequences that involve chiral organolithium reagents. A catalysis reaction requires either a ligand accelerated substitution step or a method for suppressing the rate of the uncatalyzed reaction. Furthermore, release of the ligand from the product is needed to ensure ligand turnover. A recent report of the ligand-accelerated electrophilic substitution of an α -seleno organolithium compound is a promising development in this direction.^[29]

Rational design of such processes should be preceded by a thorough mechanistic understanding of each step in the reaction pathway. Although the challenge of developing catalytic methodologies in this area is not trivial, further advances in asymmetric ligand design and an increased fundamental understanding of reaction pathways should outline possible approaches. Given the wealth and diversity of the noncatalytic chiral organolithium chemistry described herein, it appears that it is a goal worth pursuing.

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Chemical Transformations: Translation and the Periodic Table in Japan

Scott L. Montgomery*

Science and Language

Since its very beginnings, scientific knowledge has resided largely in the deposits of language. It is the written word, above all, that has allowed science to be recorded, shared, debated, standardized, passed on, and advanced. We know this, intuitively, whether we are students of the ancient manuscript or the contemporary journal. Prior to very recent times, in fact, the forms of learning we would recognize as scientific existed almost entirely in texts: science largely began and ended with inscription. Certainly there were practices involved too: in chemistry, with its alchemical past, procedures for combining and mixing of materials had to be learned, usually through demonstration and apprenticeship, and sometimes in secret. Yet none of this could have survived unless written down and studied in some way. Much depended on various crucial works, it appears, such as the *The Emerald Tablet of Hermes* (and its many versions), the Arabic *Kitab Sirr al-Asar* (Book of Secrets), or even Pliny's *Natural History*. Moreover, as we approach the modern era, with its dependence on the technology of print, the epochal work of thinkers such as Paracelsus, Boyle, and Lavoisier gained great influence by being published and—most of all—disseminated to other natural philosophers in other lands.

Scientific Translations

Once embodied in writing, knowledge becomes mobile. We say that science “advances”, but it also moves, across borders of time and place, as a result of being transferred from one people and language to another. Indeed, movements of scientific knowledge have been central to the building of modern societies—we need only think of the effects brought about by the introduction into various cultures of Archimedean mechanics, Arabic (actually Indian) numerals, the calculus, the periodic table.

How is knowledge made mobile, and thereby accessible to the greater world? Above all, through the work of translation. No less than his literary counterpart, the scientific translator has been the creator of new texts, the multiplier of sources

into new languages, and thereby the producer of new “originals” for use. Indeed, when viewed in this way, scientific translation becomes far more than the silent, word-for-word chiseling of anonymous scribes or technical “clerics”—the impoverished image so often given to this effort. In fact, over the centuries, translation has increased the great library of science many times over, and it has done this in manifold and diverse ways. Prior to the 20th century, as it happens, there were no set standards at all for how translators should perform their task or how accurate their results should be. The rendering of scientific works into new languages sometimes strove for fidelity, sometimes paraphrase, most often a mixture of the two. It employed both oral and written methods, often together. It involved individuals, families, even teams. It used for its sources original texts, edited and re-written texts, fabricated or falsely attributed texts, works already translated several or more times, works of recent vintage or those more than a thousand years old that had long ceased to exist in anything resembling their first form. As a result of all this diversity in method and material, translations of scientific works varied enormously in their quality and character. Close inspection shows that any single translation varied significantly in the degree to which it remained loyal or re-wrote an original, a variability that depended on the exact nature of the text, the knowledge and ability of the translator, and so on.

Thus, in order to accept and understand translation as a crucial historical force in science, we must also admit the rich complexities that have long surrounded it. Moreover, though it remains all too common to conceive of scientific translation as literal, mechanical work, this has never been true. Indeed, the image is a form of prejudice. Experienced (and honest) translators of scientific works today would be forced to admit that their work is more complex than simple lexical transfer. Translating science cannot avoid the responsibility of interpretation, the re-making of an original. As linguists and literary theorists have frequently pointed out, there is never a one-to-one correspondence among languages, even among those of a single “family” (e.g. the Romance languages). If there were, no use whatsoever would exist for the living, breathing translator of today: machines would have long rendered him extinct. Of course, auto-translation remains very much a dream of the present. But as anyone knows who has examined (or been forced to edit) current results in this area, it still has a long way to go; the element of interpretation cannot be wished away, algorithmically.

[*] Prof. S. L. Montgomery
1511 18th Avenue East
Seattle WA 98112 (USA)
Fax: (+1) 206-322-8597
E-mail: scott.montgomery@prodigy.net

What about historical examples, then, of how translation has worked its effects? Chemistry, in fact, provides some of the most intriguing examples. Consider, for instance, the way in which modern chemical concepts, the idea of “element” and the entire nomenclature of the periodic table, came to make their appearance in a distinctly non-western nation, in an assertively non-western language.

Between roughly 1780 and 1850, a great measure of European science, including the new chemical principles inaugurated by Lavoisier, was transferred to the island of Japan. This was a period in which those whom we might term scientists in Japan were translators above all else—such was their primary, and often their only, work. Moreover, they were translators from the Dutch—*rangaku-sha* (“scholars of Dutch Studies”). Holland, after all, remained at this time the only European nation with which Japan allowed any trade relations, and it was through Dutch translations of many English, French, Latin, and German works that Japan learned of western science. A ban on books from Europe had been lifted in 1720, and these had begun to be translated not long after. By the later decades of the 18th century, some of these translated works—specifically those on medicine—had begun to be published and made available to the scholarly community, with the result that a surge of interest in European science occurred.

In chemistry, as in other fields, there was no possibility of a simple transfer in vocabulary from western languages to Japanese or Chinese (still the language of high scholarship in Japan during this period). Many fundamental ideas and terms, including those for “element” and “chemistry”, as well as the names for many elements themselves, had to be invented, debated, and eventually accepted. No linguistic models or guides in Japanese existed for this sort of mass transfer. Instead, the responsibility fell upon the shoulders of the individual translator.

The person who took on this profound task was Yoan Udagawa, a brilliant polymath of indefatigable curiosity, energy, and productivity.^[1] Between 1820 and 1850, he produced a seminal 20-volume work on chemistry, the *Seimi Kaisō* (“Principles of Western Chemistry”), as well as books on occidental botany, zoology, history, geography, music, and mathematics. Udagawa came from a well-known family of physician–scholars trained in Chinese medicine (as were all Japanese physicians), and was led to an interest in western chemistry by two streams of influence, one ancient, the other contemporary. As a physician, Yoan had been educated in classical, herbal-based therapies and had a deep appreciation for pharmacology. His adopted father, meanwhile, was a *rangaku-sha*, contracted by the government to help translate the new books then coming from Holland, and keenly aware, it seems, of his son’s linguistic and intellectual abilities. Yoan was thus urged to master both the Chinese classics and the Dutch language, in order to be in a better position to weigh each against the other and also to present the new western science in a manner palatable to other Japanese scholars. As a young man with both conservative roots and larger ambitions, Yoan Udagawa found himself at a historical cross-roads. It

was his fate, in a sense, to contribute magnificently to the growing shift away from traditional natural philosophy, with its ancient Chinese roots, and toward a more modern, materialist science.

The *Seimi Kaisō* was a foundational work of this new science for several reasons. First, it introduced element theory, related terminology, and Lavoisierian chemistry in general. Second, it was written not in Chinese, as scholarly books commonly were up to that time, but in the native tongue, Japanese, and in a style very much intended to be accessible to the entire literate community. Third, in creating a new terminology, including the names of the elements, it did not do away entirely with pre-existing titles, such as those for important and well-known metals (gold, lead, copper, silver), but instead incorporated these into a complex and diverse system of nomenclature that even made certain concessions to Chinese natural philosophy.

What were Yoan’s actual sources? There appear to have been a fair number of them, perhaps as many as 20 separate books,^[2] from which Yoan translated sections, paraphrased others, and assembled individual chapters of his own work from these various selected pieces. The most important text he used seems to have been a Dutch work of complicated history. In simplified terms, it was a Dutch translation of a German work, *Chemie für Dilletanten* (1803), which was itself translated from William Henry’s *Epitome of Chemistry* (1803), a very successful English rendering, in paraphrased form, of Lavoisier’s own *Traité Élémentaire de Chimie* (1789). Yoan’s choice was therefore well-considered, even as a translation of a translation of a paraphrased translation.

The Periodic Table in Japanese

What, then, of his terminology? In what form did the modern elements appear in Japan? The *Seimi Kaisō* lays out a clear definition of “element”, calling it a “primitive indivisible substance”. The word the author used for this basic substance was *gensō*, a combination of two ideograms, the first of which meant “origin/beginning,” the second, “simple/essence”. This choice seems to have been partly a nod in the direction of Chinese natural philosophy, with its emphasis on fundamental ontological principles. But Yoan’s employ of the character *so* (“simple/essence”) was also a potent adaptation. Indeed, in a fair number of element names, he used this ideogram as a suffix for elements that did not exist in Japanese or Chinese: for example, *suiso*, or “water-essence”, for hydrogen; *tanso*, or “coal-essence”, for carbon, and also (an interesting historical touch), *onso*, “warmth-essence”, for the false element “calorium” proposed by Berzelius but later rejected by European chemists. The adaptation of this form comes from the Dutch/German tradition of element names, a tradition that included *Grondstoff/Urstoff* for “element” (and *Koolstoff/Kohlenstoff* for “carbon”, etc.) and that, for a variety of reasons, political in part, was never replaced with the new French nomenclature invented by Lavoisier. As a *rangaku-sha*, a student of Dutch Studies, Yoan Udagawa was also an inheritor of this terminological tradition: in entering Japan, European science was very often forced to pass through the filter of Dutch linguistic realities.

The full nomenclature of the *Seimi Kaisō*, however, was far more complex and “multicultural” than this might suggest. In total, the kinds of titles included the following: 1) traditional Japanese names, using one ideogram (e.g. *kin* for gold), that had originally come from the Chinese; 2) Japanese names with two or more characters, that were native in origin; 3) literal translations from the Dutch, e.g. *hakkin* (“white-gold”) for *witgout* (platinum); 4) translations using the suffix *so*; 5) names phonetically translated from the Latin (which had been retained in Dutch), using a sound system that had been adapted from the Chinese centuries earlier (one that employed ideograms purely for phonetic value). In total, therefore, Yoan’s nomenclature was both faithful to the preeminence of Chinese linguistic influence in Japan and also innovative in introducing new methods of naming that extended well beyond the reach of such influence.

This overall scheme, however complex, was not the final word in chemical nomenclature. Yoan had helped set a new pace, and with the opening of Japan in general to works from other nations, the terminology he inaugurated was sure to undergo some modification later on. Indeed, during the later half of the 19th century, chemical nomenclature was the subject of no small debate, with several major new schemes proposed, some loyal to ancient tradition, others to Western usage, and still others endeavoring to replace everything that had gone before with a set of new Japanese names, written purely in Japanese script (*hiragana*). Even the title for “chemistry” itself—previously (as in *Seimi Kaisō*) given as *seimi*, a phonetic adaptation from the Dutch (*Schemie*)—was fought over and eventually replaced with the word *kagaku* (“study of change”), a Chinese loan-word. Above all, however, influence from Europe remained strong—much of Yoan Udagawa’s terminology was kept intact—particularly with the influx of new works on chemistry translated from English, French, and German. Element names taken from these languages were increasingly changed from the Chinese-inspired sound system to another phonetic script native to Japan (*katakana*). Between 1880 and 1950, one sees a fascinating shift in nomenclatural favoritism aimed, first, at lingering Dutch and Latin influences, then German (to about 1920), and finally English^[3]—reflecting, in no small part, changes in perception regarding scientific preeminence and also political power worldwide.

Today, in other words, the periodic table in Japanese is a magnificent litmus of history—a chart of translated adaptation that includes ingredients from Asia and Europe both. Ancient Chinese, 17th century Latin, 18th century Japanese, and 20th century English sit shoulder-to-shoulder in this terminological dais. A testament to ingenuity, practicality, and also socio-political vulnerability, the formation of the elements in Japan is also an excellent example of how translation, as a historical process, has helped contour the scientific world of the present.

An Increased Role for the Present-Day Translator of Science

What of today, then? Such historical examples certainly have their fascinating (and too often overlooked) place in understanding the roots of modern science, but what of the

contemporary scene? Has translation a continued role, indeed a central one, in the present and future of science? After all, hasn’t English achieved a clear, dominating role as the *lingua franca* of technical communication? Haven’t scientists themselves been enormously mobile beginning in the 20th century, changing countries and languages on a large scale, whether urged by political or other circumstances? To what degree has this type of internationalization of science affected the place and importance of translation?

In fact, the role of translation is more crucial today than ever before, in part due to these very phenomena of the contemporary historical moment in science. For instance, the routine claim for a dominance of scientific English actually disguises a number of realities that have immediate implications for translating work. One of these is the truth that a great deal of science continues to be published in native languages—especially where research has a nationalistic importance or utilizes materials of local origin (China, Japan, Russia are strong examples)—a situation that results in more than one tongue being used in a particular country to publish primary science, thus creating a need for translators (the idea that scientists everywhere will renounce their mother tongues *entirely* to perform science seems naïve, particularly given the political context within which research and publication often take place). Certainly, the major portion of the secondary literature in any country is published in that nation’s language. Moreover, in cases where English is the destination language for publication, scientists in many non-English speaking nations do much (or all) of their primary research in their mother tongue and then translate (or have translated) their results into English for submission. In other words, the “dominance” of English imposes an *increased* need for translation.

English—the Lingua Franca of Science?

The international preference for English, furthermore, is also not the same for all fields; in certain disciplines (e.g. physics) it is strong, while in others (geology) it is much more variable. Finally (but this is hardly a complete list of relevant phenomena), the English used for scientific publication is not at all universal, but comes in a number of different forms—indeed, linguists today speak not of “world English” at all but of “world Englishes”. Grammar, lexical structure, terminology, and syntax exhibit no small amount of variability between journals published in India, Hong Kong, Singapore, and the U.S. As an international language, English has inevitably been adapted to different cultural-linguistic settings, and science has very much been a part of this. In brief, there is no single, standard “scientific English”; nor is there likely to be any, since this speech is itself often a subset of the English spoken or used as a professional language in different settings. To wish for such a standard is to hope for the assumption of artifice, indeed to desire an erasure of all culture from the land of science. Linguistic variability in a global language is as inescapable as changes in climate.

Let us not ignore, either, the vast area—and deep importance—of communicating research to non-scientists, including the public, the mass media, educators, political leaders, and

other decision-makers. Unless all nations of the world agree to abandon their own languages and linguistic traditions, it seems likely that translation will continue to command considerable significance in the transfer of knowledge here too. On the other hand, there are the realities of corporate science, involving patents, manuals and other documentation, reports, “white papers”, and so forth, all of which are regularly produced for specific clients and thus in a wide array of languages.

For all these reasons, the technical translator—however invisibly—is more important than ever before, a mobilizer of scientific information on a daily, even hourly basis. Only when

all nations of the world decide to abandon their own forms of speech and adopt a single, universal standard will this situation change. Is this something to wish for? But then our desire would aim at an enterprise that had left the human dimension to intelligence behind.

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A New Era in Divalent Organolanthanide Chemistry?

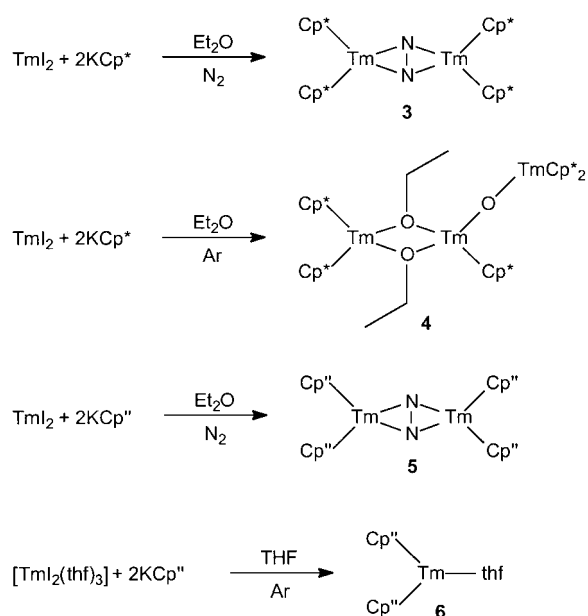
Keith Izod*

The isolation and structural characterization of the samarium(II) complex $[\text{Cp}^*_2\text{Sm}(\text{thf})_2]$ (**1**) and its unsolvated analogue $[\text{Cp}^*_2\text{Sm}]$ (**2**) has proved to be a watershed in the chemistry of the lanthanide elements.^[1, 2] In the 20 years since their initial discovery these compounds have been shown to exhibit remarkable chemistries. Their unparalleled reactivities may be illustrated by their mediation of the following selected reactions: 1) the formation of complex heterocycles from the reduction of various unsaturated organic substrates, 2) the multiple reductions of small molecules such as dinitrogen and CO, and 3) the polymerization of ethylene.^[3]

In spite of this impressive reactivity, the development of a general organometallic chemistry for divalent lanthanides has been slow to emerge, due to both the highly reducing nature of the majority of these ions and to the lack of suitable starting materials for all but the three most readily accessible Ln^{II} ions (Sm^{2+} (f^6 configuration), Eu^{2+} (f^7), and Yb^{2+} (f^{14})). For these three elements the availability of the diiodides $[\text{LnI}_2(\text{thf})_n]$ as thermally stable solids has provided a convenient entry point for the synthesis of organic derivatives. However, recent reports of the isolable and (for limited periods) solution stable diiodides of Tm^{II} , Nd^{II} , and Dy^{II} (and their crystallographically authenticated ether adducts $[\text{TmI}_2(\text{dme})_3]$,^[4b] $[\text{TmI}_2(\text{dme})_2(\text{thf})]$,^[4c] $[\text{NdI}_2(\text{thf})_5]$,^[4c] and $[\text{DyI}_2(\text{dme})_3]$ ^[4d] ($\text{dme} = 1,2\text{-dimethoxyethane}$)) suggest that an extensive organometallic chemistry for these elements may indeed be accessible.^[3c, 4] Nevertheless, the highly reducing nature of these metal centers ($E^\circ(\text{Ln}^{3+}/\text{Ln}^{2+})$ versus NHE: $\text{Tm} - 2.3$, $\text{Dy} - 2.6$, $\text{Nd} - 2.6 \text{ V}$)^[3c] and their large ionic radii require that special care must be taken in the selection of supporting ligands and reaction conditions.

The recent announcement by Evans and co-workers of the synthesis and structural characterization of the first Tm^{II} organometallic compound is testament to the importance of ligand design in the stabilization of such reactive metal centers.^[5] Evans and co-workers have previously found that attempts to prepare Tm^{II} complexes supported by the ubiquitous Cp^* ligand ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) were hampered by

reactions between the desired organothulium(II) compound and dinitrogen to give **3** or, when argon is used as blanket gas, with the ether solvent to give **4** (Scheme 1).^[6] Similar



Scheme 1. $\text{Cp}'' = \eta^5\text{-C}_5\text{H}_3\text{-1,3-(SiMe}_3)_2$.

problems have also been reported by Fedushkin and co-workers: attempts to obtain an organothulium(II) complex by the alkali metal mediated reduction of $[\text{Cp}^*_2\text{TmI}(\text{thf})]$ led to Tm^{III} products due to reaction between the Tm^{II} intermediate and the DME solvent.^[7]

The major breakthrough in the synthesis of a stable organothulium(II) compound has come through the use of the Cp'' ligand ($\text{Cp}'' = \eta^5\text{-C}_5\text{H}_3\text{-1,3-(SiMe}_3)_2$), which has different steric and electronic properties to those of Cp^* . Metathesis reactions between TmI_2 and KCp'' yield the complex $[\text{Cp}''_2\text{Tm}(\mu\text{-N}_2)\text{TmCp}''_2]$ (**5**) due, once again, to reaction of the desired Tm^{II} complex with dinitrogen.^[6] However, in contrast to the formation of **4**, when Ar is used as blanket gas the organothulium(II) complex $[\text{Cp}''_2\text{Tm}(\text{thf})]$ (**6**) is isolated in high yield (Scheme 1).^[5] These reactions clearly demonstrate, not only the high reactivity of organothulium(II) compounds, but the importance of utilizing the appropriate ligands, solvent, and reaction conditions for their synthesis.

[*] Dr. K. Izod
Department of Chemistry
Bedson Building
University of Newcastle
Newcastle upon Tyne NE1 7RU (UK)
Fax: (+44) 191-222-6929
E-mail: k.j.izod@ncl.ac.uk

Evans and co-workers also reported the isolation of the Dy^{III} complex [Cp₂'Dy(μ -N₂)DyCp₂'] from the reaction between DyI₂ and Cp'K in diethyl ether under nitrogen.^[5] This clearly indicates the intermediacy of a Dy^{II} organometallic, although such an intermediate has yet to be isolated. It will be interesting to see whether, using the same reaction conditions as those used for the synthesis of **6**, the first Dy^{II} organometallic compound can be prepared, or whether the greater size and increased reduction potential of Dy^{II} will necessitate changes in the ligand and/or the reaction conditions to effect complex stabilization. The spectroscopic characterization and subsequent crystallization by Lappert and co-workers of compounds formulated as containing La^{II},^[8] obtained by alkali metal reduction of [Cp₃'La^{III}], suggests that even highly reducing La^{II} organometallic compounds may be readily accessible, provided that the correct supporting ligands and reaction conditions are chosen (E° (La³⁺/La²⁺) – 3.1 V versus NHE).^[3c]

Lanthanide(II) compounds now occupy a special place in the armoury of reagents available to the synthetic organic chemist due to their extremely useful redox potentials, their excellent functional group tolerance and the impressive stereo- and regioselectivities of many of their reactions.^[9] Preliminary studies of the reduction chemistry of TmI₂ and DyI₂ have already indicated that these compounds have enormous potential as reagents in organic synthesis.^[4d, 10] It remains to be seen whether new organolanthanide(II) compounds such as **6** will one day join the ranks of useful reagents.

Although they represent a significant advance in organolanthanide chemistry, the results outlined above beg several questions: 1) will it be possible to isolate organometallic compounds of the more reducing Ln^{II} ions such as Dy^{II} and Nd^{II} and, if so, to what extent must the ligand environment be modified in order to stabilize these highly reactive metal centers? 2) how will the reaction chemistries of **6** and related complexes compare with those established for **1** and **2**? and 3)

will this chemistry be limited to sterically demanding cyclopentadienyl ligands such as Cp' or will it be possible to further extend this range of compounds to include new σ -bonded organolanthanide(II) compounds?

Whatever the prospects for these new organolanthanide(II) compounds, it is evident that the future holds many challenges for the synthetic lanthanide chemist. We are on the brink of an exciting new era in organolanthanide chemistry which is certain to yield many novel compounds and unusual reactions.

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Catalytic, Enantioselective Syntheses of β -Lactones—Versatile Synthetic Building Blocks in Organic Chemistry

Christoph Schneider*

β -Lactones (2-oxetanones) combine the structural feature of a masked aldol product with the exceptional reactivity of a strained ring system that may be readily opened by nucleophiles.^[1] Whereas soft nucleophiles typically add to β -lactones

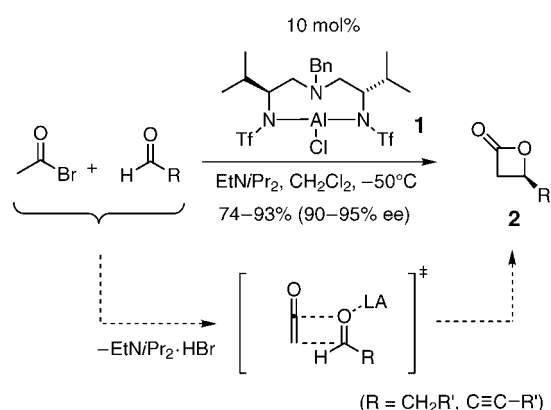
at the C(alkyl)–O bond with inversion of configuration, thereby furnishing chiral β -functionalized carboxylic acids, hard nucleophiles cleave the C(acyl)–O bond and unmask the aldol structure. Considering the significant synthetic value of β -lactones and the presence of this moiety in a number of biologically interesting natural products,^[2] it is not surprising that great effort is currently being made to synthesize optically active β -lactones selectively and efficiently.^[3]

The most direct synthesis of β -lactones involves the reaction of a ketene and an aldehyde which may proceed

[*] Priv.-Doz. Dr. C. Schneider
Institut für Organische Chemie
Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-399660
E-mail: cschnei1@gwdg.de

either by way of a concerted [2+2] cycloaddition (HOMO(ketene)–LUMO(aldehyde) interaction) or, catalyzed by nucleophiles such as amines, through a stepwise aldol–lactonization reaction. The process developed by Wynberg and Staring in 1982^[4] using cinchona alkaloids as nucleophilic catalysts—one of the earliest catalytic, enantioselective reactions—is an exceptional example for the latter variant which unfortunately allows only very reactive aldehydes, such as chloral, to be used as reaction partners. Recently however, substantial progress towards the development of more broadly applicable catalytic, enantioselective syntheses of β -lactones has been reported by several groups.

Nelson et al. developed the chiral, C_2 -symmetric aluminum complex **1**, which was shown to be capable of catalyzing ketene–aldehyde cycloadditions under very mild conditions and in high yields and enantioselectivities (Scheme 1).^[5] The

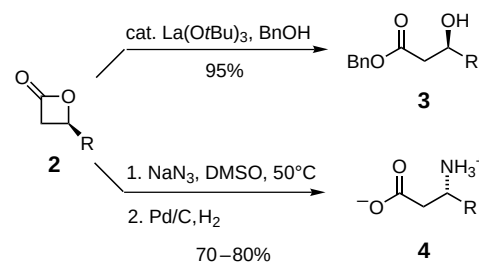


Scheme 1. [2+2] Cycloadditions of in situ generated ketenes and aldehydes according to Nelson et al.^[5] Tf = trifluoromethanesulfonyl.

ketene component is generated in situ from acetyl bromide by treatment with Hünig's base and treated directly with the aldehyde complexed by the chiral Lewis acid **1** (10 mol %). Especially α -unbranched and acetylenic aldehydes have proved to be good substrates for this process, furnishing the optically active 2-oxetanones **2** typically in yields of 80–90% and enantioselectivities of 90–95% *ee*. By using propionyl bromide as ketene precursor in this scheme, 3,4-disubstituted 2-oxetanones are accessible with excellent *cis* diastereoselectivity as well.^[6]

The free acetate aldol products **3** were obtained through reaction with alcohols catalyzed by $\text{La}(\text{O}i\text{Bu})_3$. Alternatively, the β -lactones **2** may be treated with NaN_3 in DMSO which resulted in the formation of β -azidocarboxylic acids with complete inversion of configuration. The latter were then hydrogenated with Pd/C to valuable β -amino acids **4** (Scheme 2).^[7]

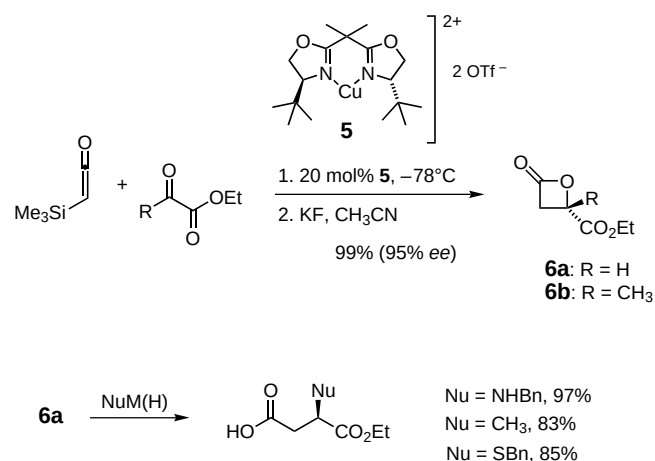
Crystallographic analysis of the aluminum triamine complex **1** revealed that the Lewis acidity of the a priori electron-rich complex stems from a trigonal-monopyramidal geometry around the aluminum center which leaves a fifth ligation site ideally disposed to accept the aldehyde. The X-ray structure of the **1**-DMF complex having a trigonal-bipyramidal geometry nicely supports this assumption. Interestingly, complexes



Scheme 2. Transformation of β -lactones **2** into acetate aldol products **3** and β -amino acids **4**.

lacking the additional heteroatom in the tether or complexes with a longer tether do not exhibit catalytic activity.^[8]

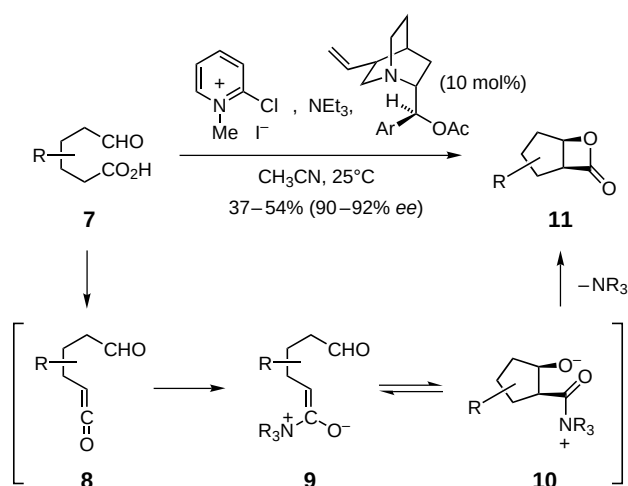
Evans et al. utilize C_2 -symmetric copper(II)-bisoxazoline complexes **5** as chiral catalysts for the [2+2] cycloaddition of the more stable trimethylsilyl ketene with ethyl glyoxylate which affords the optically active β -lactone **6a** in very good yield and enantioselectivity (Scheme 3).^[9] The observed



Scheme 3. [2+2] Cycloadditions of trimethylsilyl ketene and α -dicarbonyl compounds according to Evans et al.^[9]

enantioselectivity is assumed to be derived from a double coordination of the chiral metal complex to the α -dicarbonyl moiety of the aldehyde and a square-planar geometry around the copper ion. Other α -oxygenated carbonyl compounds such as ethyl pyruvate and α -diketones are also good substrates for the cycloaddition and yield the corresponding β -lactones in good yields and enantioselectivities. The trimethylsilyl group is typically cleaved with fluoride after completion of the reaction. Furthermore, a series of stereospecific ring-opening reactions were conducted on the β -lactone **6a**, which gave rise to a range of optically active carboxylic acids (Scheme 3).

Romo et al. have synthesized some optically active bicyclic lactones **10** in moderate yields and very good enantioselectivities taking advantage of the cinchona alkaloid catalyzed aldol lactonization reaction (Scheme 4).^[10] In a further development of the approach adopted by Wynberg and Staring they utilize ω -oxocarboxylic acids **7** and treat them with 2-chloro-*N*-methylpyridinium iodide (Mukaiyama reagent)

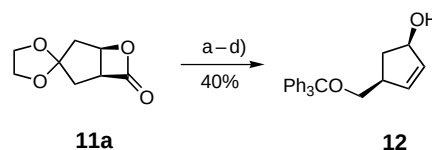


Scheme 4. Cinchona alkaloid catalyzed aldol–lactonization sequence to bicyclic β -lactones **11** according to Romo et al.^[10]

and NEt_3 to furnish in situ the ω -oxo ketenes **8**. This strategy has two advantages: it avoids the otherwise necessary use of a ketene generator, and the intramolecular reaction course allows the employment of not specifically activated aldehydes. *O*-Acetyl quinidine (10 mol %) now adds in situ to ketene **8**, and the resulting ammonium enolate **9** engages the aldehyde in an intramolecular aldol reaction to yield aldolate **10**, which cyclizes to β -lactone **11** with concomitant regeneration of the chiral catalyst. The rate- and configuration-determining step is presumably the cyclization to the β -lactone, while the aldolate is formed reversibly. Owing to ring strain considerations only *cis*-fused bicyclic rings are formed, the *trans*-aldolates presumably revert back to the ammonium enolates in a retro-aldol reaction.

Bicyclic compounds **11** are characteristic structural elements of various natural products, such as spongiolactone,^[2] and after ring-opening useful intermediates for the synthesis of pharmacologically interesting compounds. For this purpose

11a was reductively opened and the enone moiety liberated through acid-catalyzed hydrolysis and elimination. Upon DIBAH reduction the highly enantiomerically enriched cyclopentenol **12** was obtained, which has been used previously as an intermediate in the synthesis of the antiviral, carbocyclic nucleoside aristeromycin (Scheme 5).

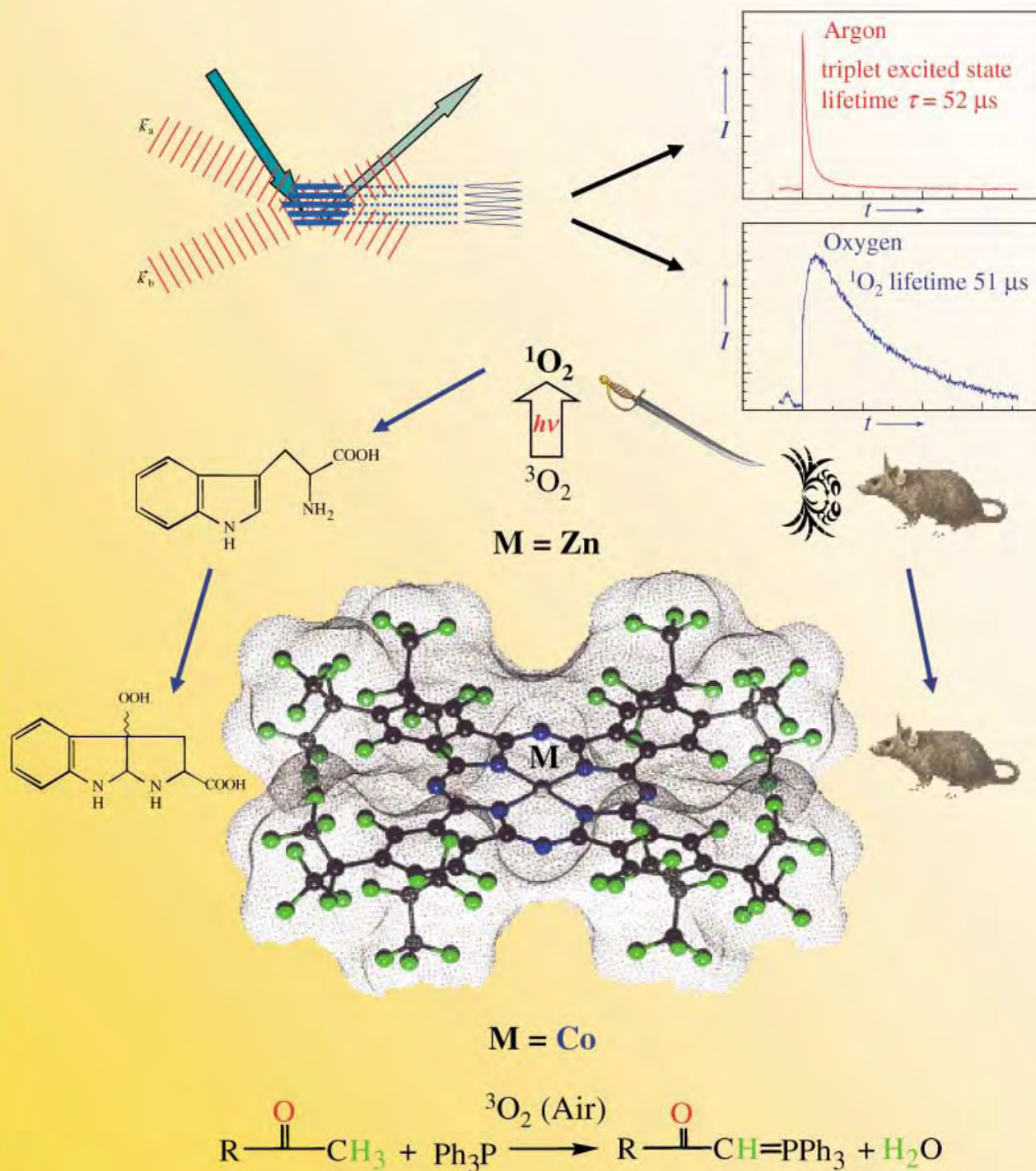


Scheme 5. Synthesis of an intermediate for aristeromycin from **11a**. a) $\text{BH}_3 \cdot \text{SMe}_2$, THF; b) 1N HCl, THF; c) Ph_3CCl , CH_2Cl_2 ; d) diisobutylaluminum hydride (DIBAH), THF.

In conclusion, these new methods for the catalytic, enantioselective synthesis of β -lactones constitute a significant advancement of synthetic methodology and should bring about more synthetic applications of β -lactones. The search for even more broadly applicable and more selective catalysts and processes will surely continue.

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Perfluoroalkyl Phthalocyanines



For more information see the following pages.

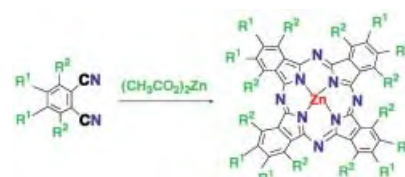
Introduction of Bulky Perfluoroalkyl Groups at the Periphery of Zinc Perfluorophthalocyanine: Chemical, Structural, Electronic, and Preliminary Photophysical and Biological Effects**

Barbara A. Bench, Andrew Beveridge,
Wesley M. Sharman, Gerald J. Diebold,*
Johan E. van Lier,* and Sergiu M. Gorun*

Phthalocyanines (Pcs) are a class of molecules that continue to elicit interest as pigments and dyes, nonlinear optical media, chemical sensors, catalysts, optical storage media, and phototherapeutic drugs.^[1] Peripheral substituents have been used to tune the steric and electronic features of phthalocyanines, to yield both electron-rich and electron-poor species, the latter including the important class of halogenated phthalocyanines. The peripheral substituents for the electron-poor compounds, however, are restricted almost exclusively to the halogens themselves, which translates into both poor solubility in organic solvents, paucity of substituent types, and a restriction of the molecular geometry to planar architectures. Consequently, the structural diversity of such electron-poor phthalocyanines is extremely limited and their solid-state structural characterization at atomic level is apparently unknown.^[2] Furthermore, planar phthalocyanines tend to aggregate by π - π stacking interactions or single-atom bridges, a disadvantage if high solubility or single-site isolation is desired, for example, for homogeneous catalysis. The introduction of bulky, peripheral substituents encourages the formation of isolated, monomeric species. If such substituents are perhalogenated, preferably perfluorinated, materials that are both soluble and resistant to self-oxidation might result. Such materials may be suitable for homogeneous catalysis under harsh conditions, which include the presence of reactive species such as singlet oxygen and free radicals.

We report here the facile synthesis and single-crystal X-ray structural characterization of $F_{64}PcZn$, the first nonplanar, biconcave, halogenated metallophthalocyanine. We also report the chemical, electronic, and preliminary photophysical and biological effects of the introduction of bulky, perfluorinated substituents (R^F groups). The above effects are likely to be found in related molecules belonging to the same class but yet to be prepared.

Perfluoro-(4,5-di-isopropyl)phthalonitrile,^[3] **1**, was melted with zinc acetate at 180 °C to yield a blue-green solid. Chromatographic purification yields a blue material, the intensely colored solutions of which in organic solvents exhibit UV/Vis spectra characteristic of phthalocyanines. The ¹³C and ¹⁹F NMR spectra of this material have the same number of peaks as **1**, but are shifted by up to $\delta = 42.1$ for the nitrile C and $\delta = -7.7$ for the aromatic F atoms, respectively. These changes indicate the formation of $[F_{64}PcZn(\text{acetone})_2]$ (**2**; Scheme 1).



Scheme 1. Synthesis of $[F_{64}PcZn(\text{acetone})_2]$ (**2**) (acetone molecules omitted); $R^1 = CF(CF_3)_2$, $R^2 = F$.

Complex **2** readily forms large single crystals, a likely consequence of the peripheral bulky R^F (iC_3F_7) groups that both decrease π - π stacking interactions and increase solubility. The X-ray structure (Figure 1),^[4] reveals a zinc-centered Pc ring, the orientation of the CF_3 groups of the iC_3F_7 substituents above and below the phthalocyanine plane, and the axial coordination of two acetone molecules. The presence of ligands above and below the phthalocyanine plane imparts an overall bulky or biconcave character to the complex. Crystallographically authenticated acetone solvates are not known for any other Pc compounds, while sterically

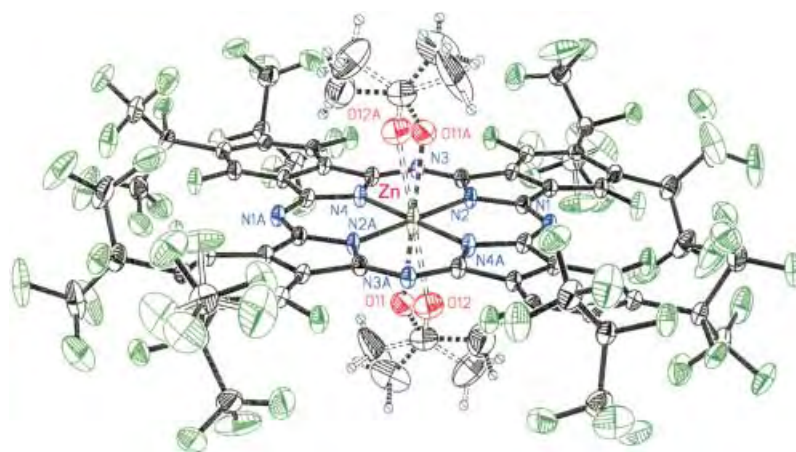


Figure 1. Molecular structure of **2** with thermal ellipsoids set at 30% probability level. Two symmetry equivalent axial acetone molecules are disordered over two positions. Selected bond lengths [Å] and angles [°]: Zn-N2 2.008(2), Zn-N4 2.004(2), Zn-O11 2.446(10), Zn-O12 2.376(10); N2-Zn-O12 83.3(2), N4-Zn-O12 94.3(2); F green, N blue, O red, C gray.

[*] Prof. Dr. G. J. Diebold, Prof. Dr. S. M. Gorun,
B. A. Bench, A. Beveridge
Department of Chemistry
Brown University
Providence, RI 02912 (USA)
Fax: (+1) 401-863-2594
E-mail: Gerald_Diebold@Brown.edu
Sergiu_Gorun@Brown.edu

Prof. Dr. J. E. van Lier, W. M. Sharman
Department of Nuclear Medicine and Radiobiology
University of Sherbrooke
Sherbrooke, QC J1H 5N4 (Canada)
Fax: (+1) 819-564-5442
E-mail: Jvanlier@courrier.usherb.ca

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unencumbered, strictly planar PcZn complexes are tetra- and penta-, but not hexacoordinated.^[2] Despite longer Zn–N bonds ($2.006 \pm 0.002(3)$ Å) in **2** compared with planar, tetracoordinated PcZn^[5a] and Zn naphthalocyanine ($1.980 \pm 0.002(2)$ Å),^[5b] the Pc ring is perfectly planar. No π – π stacking is observed in solid state. Complex **2** is surprisingly stable as a solvated solid. A crystal of **2** gave the same X-ray structure (including the axial acetone molecules) after storage in air for one year. We ascribe the stability of the metal–acetone bonds to the bulky R^F groups, which lower the metal charge density (favoring donation from the axial ligands) and provide some steric hindrance. A favorable packing may be more important in the solid-state. The same electronic and steric factors stabilize acetone in the analogous paramagnetic cobalt complex^[6] and make acetone competitive with O₂ for the copper site in fluorinated tris(pyrazolyl)borate complexes.^[7] Unlike **2**, the strictly planar zinc perfluorophthalocyanines [F₁₆PcZn] (**3**; of similar electronic structure, R¹ = R² = F in Scheme 1)^[8] and protio PcZn^[9] do not retain solvent when precipitated from acetone. Thus, the coordination differences can be ascribed at least in part to the decrease in steric dimensionality (that is from nonplanar, biconcave to planar).

The Q band of **2** (686 nm in acetone), is 23 nm bathochromically shifted from the Q band of **3** (665 nm). A similar bathochromic trend for the Q band is observed in pyridine, a solvent that favors deaggregation: **2** and **3** absorb at 698 and 679 nm, respectively.

The molar extinction coefficient of **2** is significantly larger than that of **3**, 1.73×10^5 versus 2.9×10^4 M^{−1} cm^{−1}. The first reduction potential of **2** shifts to -0.25 V, from -0.84 V in **3**.^[10] Collectively, the UV/Vis and electrochemical results suggest a narrowing of the HOMO–LUMO gap and an increase in electronegativity of the substituents upon perfluoroalkylation.

These changes could be rationalized by considering primarily the electronic effects of the peripheral substituents, since in both **2** and, presumably **3**, the aromatic macrocycle retains its planarity in solution. Hammett constants for *i*C₃F₇ are not reported, but values for CF₃ (from benzene derivatives) could be used as an approximation for Pc.^[11a] For F and CF₃, the inductive effect values are 0.74 and 0.64, while the resonance values are -0.60 and 0.76 , respectively.^[11b] Both CF₃ and F have σ withdrawing effects, but the resonance effects have the opposite sign, being larger by 0.16 for F in absolute terms. The increase in electron density in **2** relative to **3** because of the $+0.1$ decrease in inductive effect in changing from F (0.74) to CF₃ (0.64) is more than compensated by the resonance contributions with the exchange of the -0.60 contribution of F for the $+0.76$ of CF₃. In the framework of Gouterman's four orbitals model,^[12] the LUMO (e_g) is stabilized more than the HOMO (a_{1u}) by the loss of aromatic fluorine conjugation. The large extinction coefficient of the Q band in **2** establishes that R^F derivatization maintains the nondegeneracy of the a_{1u} and a_{2u} orbitals, and hence the applicability of Gouterman's model.

Generally, ring distortions notwithstanding, the higher degree of fluorination achieved by increasing the ratio of ring-attached R^F to aromatic F groups in this Pc unit is likely

to result in red-shifted Q bands and increase molecular electron deficiency. An alternative method for fluorine enrichment of Pcs, namely elongation of the R^F groups, will have a significantly smaller effect upon the above parameters, which will include smaller shifts in the $\lambda_{\max}$ and first reduction potentials. This latter notion is in line with the classical view of the inductive effect, whereby electronic influences progressively decrease as the chain is elongated. Considering the potential versatility of Scheme 1 and demonstrated ring planarity of **2** and its cobalt analogue,^[6] this generalization may be valuable as a synthetic strategy.

The peripheral bulkiness is expected to prevent π – π stacking not only in solid-state but also in solution, thus favoring single-site isolation. Correy–Pauling–Koltun (CPK) models suggest that the lower limit of cofacial approach of two molecules of **2**, rotated by 45° to minimize steric repulsions, is about 3.9 Å. Tilting and/or shifting may slightly reduce this limit, but both distortions place R^F groups above the aromatic ring and block metal coordination. Consistent with this model, the ¹⁹F NMR spectra of **2** is concentration independent; the Lambert–Beer law of the Q band, a sensitive probe of aggregation, is also obeyed up to 10 μ M, unlike the electronically similar, but planar **3**. No significant NMR signal or UV/Vis absorption band broadening is observed either.

The effect of R^F substitution upon the activation of O₂ by **2**, and its oxidation resistance was probed by testing **2** as a sensitizer for the photochemical production of ¹ Δ_g O₂ from O₂. If **2** were to function as photosensitizer, a preliminary requirement is that the lifetime, τ , of its triplet excited state T₁, is sufficiently long for the productive T₁–³O₂ interactions to occur. We have measured τ for **2** and **3** by a transient grating method that relies upon the photoacoustic effect produced by the nonradiative deactivation of excited molecular states and a refractive index change resulting from the transfer of population from the ground state to T₁. The decay of the thermal mode of the grating, measured with a probe laser, yields τ .^[13] Our method gives for the lifetime of singlet oxygen in acetone 51 ± 3 μ s, consistent with the literature values (50.5 , 51 , and 51 μ s).^[14] In acetone, in the absence of oxygen, τ is 52 ± 3 μ s for **2** (at 10 μ M) and < 1 μ s for **3**.^[15] The observed difference in τ , which is known to decrease with increased aggregation, further confirms that R^F substitution results in less aggregation. The photochemical production of ¹ Δ_g O₂ was independently corroborated using a standard L-tryptophan photooxidation test, which can distinguish between free radicals and singlet-oxygen products.^[16] Both **2** and **3** produce peroxides, thus proving that **2** is a photosensitizer. Significantly, bleaching was not observed during our chemical or photochemical experiments with **2**, thus confirming its robustness.

These data suggests that **2** might be useful for applications that use ¹ Δ_g O₂. Considering also the favorable bathochromic shift, solubility, excited-state lifetime and lack of aggregation of **2** in the context of the known photodynamic activity of phthalocyanines,^[17] the biological consequences of the non-planar, biconcave geometry were preliminarily evaluated in vivo. Using EMT-6 mammary tumors in mice, **2** produced 100 % tumor regression at a dose of 2.5 μ mol kg^{−1}. In the case

of **3**, a dose of 5 $\mu\text{mol kg}^{-1}$ induced 60 % regression.^[18] These results suggest that the introduction of bulky perfluoroalkyl groups results in higher tumor regression at lower photosensitizer doses; the molecular and pharmacological reasons for the differences between **2** and **3** in vivo remain to be elucidated.

In summary, our results provide a simple (classical) yet efficient approach to nonplanar perhalogenated phthalocyanines, of which $[\text{F}_{64}\text{PcZn}]$ is only the first representative. Other metals and R^{F} groups will yield compounds with a diversity of size, shape, and depth of fluorinated cavities around a reactive metal center. Their thermal, photochemical, and chemical stability, coupled with their potential synthetic versatility and favorable solubility, suggest that this class of molecules might be effective for photophysical, chemical, and perhaps, medical uses. Applications requiring stability under harsh conditions and/or aggressive reagents, or solubility in nonconventional solvents might be considered.

Experimental Section

2: A mixture of zinc acetate (0.123 g, 0.668 mmol) and **1**, (1.337 g, 2.67 mmol) was heated under Ar at 180 °C for 60 min. Chromatography on silica gel using 20–30 % acetone/hexanes, followed by diffusion of hexanes into an acetone solution gave crystalline **2** in 21 % yield; m.p. > 300 °C; FAB MS $[m/z]$ 2064.84 $[M^+]$. Elemental analysis: calcd (%) for $\text{ZnC}_{63.5}\text{H}_{15}\text{N}_8\text{O}_{2.5}\text{F}_{64}$: (Zn) 34.49, H 0.68, N 5.07; found: C 34.38, H 0.73, N 5.09. The extra half acetone molecule was not detected crystallographically. ^{19}F NMR (376.497 MHz, $[\text{D}_6]\text{acetone}$, CFCl_3): $\delta = -71.3$ (6F), -103.9 (1F), -164.6 (1F); ^{13}C NMR (100.613 MHz, $[\text{D}_6]\text{acetone}$): $\delta = 154.6$, 152.0, 130.9, 121.5, 117.5, 95.2. UV/Vis [nm] (log ϵ), acetone, 322 (4.38), 396 (4.56), 620 (4.42), 686 (5.24).

Biological tests: Suspensions of **2** or **3** in 10 % CRM (CRM = cremofor) were administered intravenously. The tumors were illuminated with 650–700 nm light (1 kW Xenon lamp, LL650 and LS700 filters) at fluence rates of 200 mW cm^{-2} , 400 J cm^{-2} per tumor. Absence of a palpable tumor three weeks post irradiation was considered regression.

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Synthesis and Structure of a Biconcave Cobalt Perfluorophthalocyanine and Its Catalysis of Novel Oxidative Carbon–Phosphorus Bonds Formation by Using Air**

Barbara A. Bench, William W. Brennessel, Hyun-Jin Lee, and Sergiu M. Gorun*

One of the major challenges of modern chemistry, homogeneous aerobic oxidations, poses the additional challenge of designing suitable catalysts that are not only active, but resist self-oxidation as well. For transition metal complexes, this

[*] Prof. Dr. S. M. Gorun, B. A. Bench, H.-J. Lee
Department of Chemistry
Brown University
Providence, RI, 02912 (USA)
Fax: (+1) 401-863-2594
E-mail: Sergiu_Gorun@Brown.Edu
W. W. Brennessel
Department of Chemistry
University of Minnesota
Minneapolis, MN, 55455 (USA)
Fax: (+1) 612-626-7541

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means shifting the chemistry from ligand oxidation (internal substrate) to oxidation of an external substrate. In addition, the replacement of byproduct-generating or stoichiometric oxidation reactions with catalytic ones is preferable, and environmentally benign.

We have recently reported that replacing all the C–H groups adjacent to the copper site of a hemocyanine model by C–F groups leads to reversible O₂ binding at ambient conditions without ligand decomposition.^[1a, b] We extend this strategy from non-heme to heme-type complexes and report the first peripherally substituted perfluorinated cobalt phthalocyanine. In both this and a related zinc analogue, (preceding paper)^[1c] the bulky substituents induce a nonplanar, biconcave character relative to the planar, unsubstituted perhalogenated metallophthalocyanines. We also report that the cobalt complex catalyzes the oxidative formation of carbon–phosphorus double bonds. Porphyrin^[2] and phthalocyanine (Pc) based^[2a, 3] complexes are known to catalyze the oxidation of various organic substrates, but they do not catalyze this reaction, which to the best of our knowledge is not known to occur oxidatively.

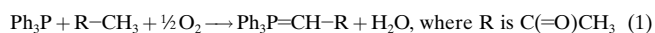
The cobalt complex, [F₆₄PcCo(acetone)₂] (**1**), was prepared by treating perfluoro-(4,5-di-isopropyl)phthalonitrile^[4] with cobalt acetate and crystallizing the product from acetone. This strategy yields a single isomer, unlike the direct free-radical substitution of fluorine in cobalt perfluorophthalocyanine [F₁₆PcCo] by linear alkyl groups, which yields an ill-defined mixture of isomers of unknown structures and composition.^[5]

The steric interactions of the *ortho* iC₃F₇ groups observed in the dinitrile precursor^[4] and the zinc structures are maintained;^[1c] the minimum energy conformation of the two methine fluorine atoms results in orientation of the CF₃ groups above and below the aromatic ring (Figure 1 b), which creates a pocket in which acetone resides (Figure 1 c). The cobalt complex **1** is deep blue and, in comparison with the parent cobalt phthalocyanine [H₁₆PcCo], or cobalt perfluorophthalocyanine [F₁₆PcCo], significantly more soluble in organic solvents. Large single crystals of **1** form readily,^[6] in contrast to strictly planar halogenated phthalocyanines. The phthalocyanine ring is planar, with the cobalt atom at its geometric center. The Co–O bond (2.314 Å) is longer than the average Co^{II}–O(acetone) bond (2.196 Å; range 2.177–2.289 Å) of the three reported cobalt(II)–acetone com-

plexes.^[7–11] Despite the long Co–O bonds, **1** does not lose solvent in the solid state at ambient conditions. The other bond lengths and angles appear normal, but a comparison with other fluorine-substituted phthalocyanine structures cannot be performed since none are reported.^[7] The van der Waals surface of **1**, Figure 1 c, defines the “Teflon-coated” fluorine-lined cavity around the metal center. In comparison with aromatic C–F groups, the exclusively aliphatic C–F groups (present also on the surface of Teflon coatings), adjacent to the cobalt, are less susceptible to nucleophilic attack and confer enhanced chemical and thermal robustness to the immediate metal environment. Two symmetry-related acetone molecules reside in the fluorine-lined cavities. Because of the sp² hybridization of the coordinated carbonyl oxygen atom, only one CH₃ group of each acetone protrudes outside and is thus exposed to the environment. In contrast to the zinc structure,^[1c] the acetone in the cobalt complex appears more ordered.

Addition of excess triphenylphosphane under ambient conditions to a solution of **1** in acetone triggers an immediate color change from blue to purple. The characteristic 668 nm Q-band absorption of **1** shifts 42 nm to 710 nm. Evaporation of the acetone solution gives purple X-ray quality crystals of the [F₆₄PcCo(1-triphenylphosphoranylidene-2-propanone)₂] (**2**; Figure 2).^[12]

The structure reveals that triphenylphosphane has coupled with both coordinated acetone molecules of **1** to form two molecules of the keto-stabilized ylide [Eq. (1)], 1-triphenylphosphoranylidene-2-propanone (henceforth called ylide), part of the complex [F₆₄PcCo(ylide)₂] (**2**).



This reaction does not occur in the absence of air. Both *trans* acetone molecules couple, in overall quantitative yield, based upon cobalt. In general, coordinated acetone is labile, even if the metal is complexed by sterically demanding ligands. In particular, the reaction of Ph₃P with such complexes results in acetone substitution. For example, Kläui's O₃-tripodal ligand, [(η⁵-C₅H₅)Co{P(=O)(OMe)}₃] (**L**), forms half-sandwich [LM(anion)(acetone)] complexes, M = Co^{II} and Ni^{II}.^[10, 11] The acetone of the nickel complex, isostructural with the cobalt complex, is easily substituted by Ph₃P. In

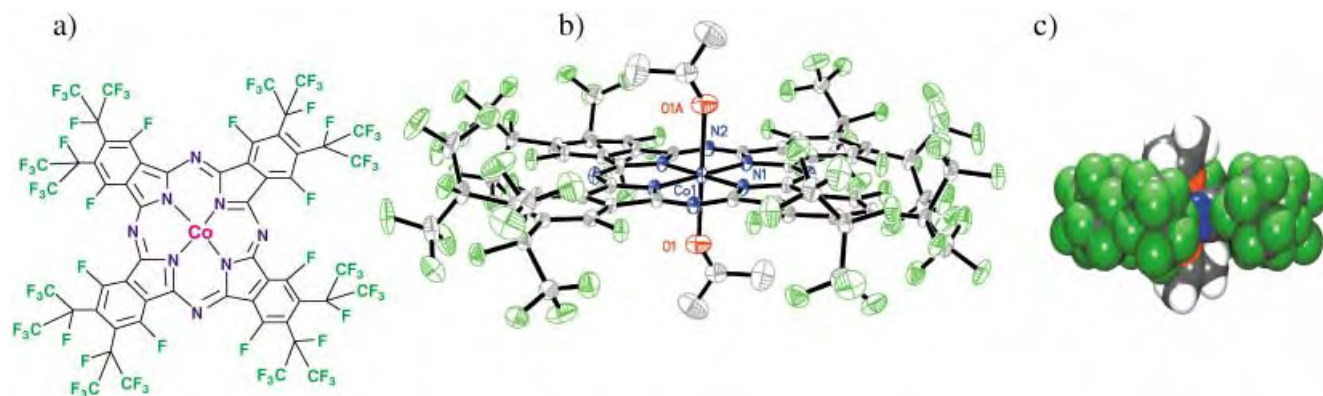


Figure 1. 1: a) structural formula (acetone molecules omitted); b) X-ray structure with thermal ellipsoids set at 30% probability (H atoms of the acetone molecules are omitted); c) space-filling representation viewed along the phthalocyanine ring; F green, N blue, O red, C gray, H white.

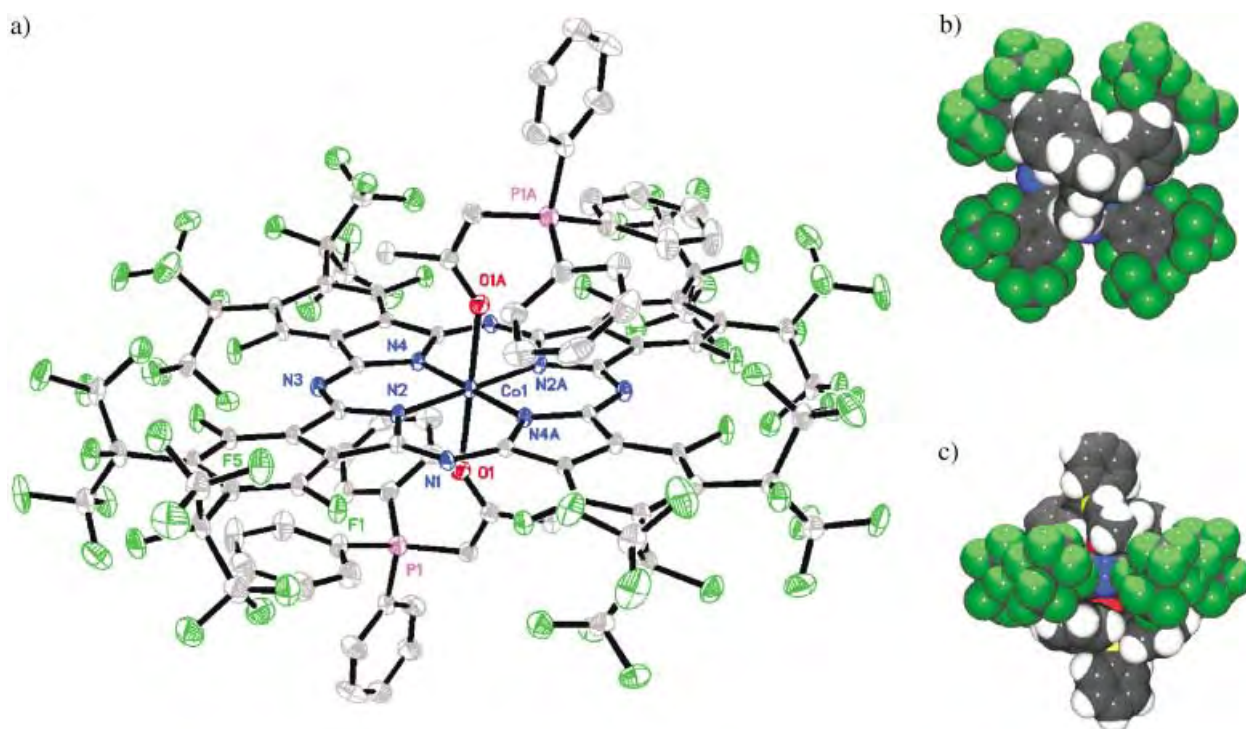


Figure 2. 2: a) X-ray structure with thermal ellipsoids set at 30% probability (H atoms omitted); b) space-filling representation viewed perpendicular to the phthalocyanine ring; c) space-filling representation viewed along the phthalocyanine ring; F green, N blue, O red, C gray, P purple.

contrast, the acetone molecules of **1** react with Ph_3P , rather than being replaced by it.

The geometry of the F_{64}PcCo moiety of **2** is similar to that of its $[\text{F}_{64}\text{PcCo}(\text{acetone})_2]$ precursor. The 1.259(5) Å $\text{C}=\text{O}$ and 1.723(4) Å methine carbon–phosphorous bonds in **2** are slightly below the 1.275–1.333 Å (average 1.292 Å) and 1.732–1.773 Å (average 1.752 Å) values observed for the other three, Ti,^[13] Sn,^[14] and Pd,^[15] structurally characterized metal–ylide compounds; in contrast, the methine carbon–carbonyl carbon bonds are longer, 1.383(5) Å versus 1.333–1.366 Å (average 1.353 Å). Taken collectively, the structural differences suggest only a small negative charge (if any) on the coordinated carbonyl oxygen atom. On the other hand, the infrared spectrum of **2** shows a ν_{co} band at 1509 cm^{-1} , a value which is 34 cm^{-1} lower than the corresponding ν_{co} band of the free 1-triphenylphosphoranylidene-2-propanone (1540 cm^{-1})^[16]. This shift suggests the presence of a significant negative charge on the coordinated carbonyl oxygen atom. Despite the low ν_{co} value the ylide unit in **2** appears to be geometrically closer to the free ylide (the X-ray structure of which has not been reported), as is consistent with the relatively long Co–O bonds (2.221(3) Å).

We ascribe the relative stability of the ylide complex (which allowed its isolation) to the electron-withdrawing effect of the fluorine groups, which enhances the Lewis acidity of the metal center, combined with the effect of the tight fit of the ylide inside the F_{64}PcCo pocket. One of the phenyl rings of the ylide group, which is almost parallel to the Pc ring (16° dihedral angle, Figure 2b) and only 3.8 Å away from it may provide additional stabilization by π – π stacking interactions. Because of the ylide penetration inside the F_{64}PcCo cavity, a second phenyl ring also tends to become parallel with the Pc ring

(Figure 2b, c). As a result, its contact with the first ring, as measured by the *meta* C(phenyl)–C(phenyl) inter-ring distance, is 3.455 Å, a value lower than that of 84.7% of the over 2100 *meta*–*meta* contacts reported^[7] for Ph_3P . The tight fit (steric repulsions), however, may prevent the carbonyl oxygen atom from freely approaching the metal center and thus hampers the formation of a stronger cobalt–oxygen bond. For the same steric reason the Ph_3P group may not be able to penetrate sufficiently deep inside the cavity to coordinate to the metal center. A contributing factor may be the mismatch between the three-fold symmetry of Ph_3P and four-fold symmetry of the cavity, which prevents the alignment of the Ph_3P phenyl rings along the cavity grooves (see Figure 2b, c).

Notably, there are no first-row transition metal ylide complexes structurally characterized; the reaction of ylide with CoCl_2 does not result in coordination.^[17]

The similar geometry and position of the ylide (product) and acetone (reactant), on the one hand, suggests that 1) the coupling with Ph_3P does not require a significant reorganizational activation energy of the precursor and 2) only the exposed methyl group is available for coupling despite the large excess of Ph_3P . The similarity in the geometry of the coordinated and free ylide, on the other hand, suggests that the coordinated ylide might be labile in solution. Complexes **1** and **2** are in equilibrium in acetone; addition of excess coordinating solvent to **2** results in the liberation of the ylide and regeneration of **1**. Column chromatography allows the facile separation of the ylide. After removing the excess acetone by rotoevaporation the equilibrium is shifted back towards **2** and the process can be repeated as long as there is free Ph_3P . This catalytic cycle, which can be monitored by UV/Vis spectroscopy, has been performed numerous times, each

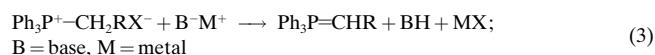
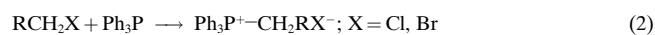
time producing the ylide complex **2** in quantitative yield (based upon the cobalt complex). No decomposition of the catalyst was observed.

Both the appropriate metal and the steric bulkiness of the ligand appear essential for catalysis. Thus, neither the sterically analogous $[\text{F}_{64}\text{PcZn}(\text{acetone})_2]$,^[1c] nor the unhindered, *two-dimensional* cobalt perfluorophthalocyanine complexes $[\text{F}_{16}\text{PcCo}]$ and $[\text{H}_{16}\text{PcCo}]$ form 1-triphenyl-phosphoranylidene-2-propanone with Ph_3P even after several days under reflux in acetone. Saturated acetone solutions of either $[\text{F}_{16}\text{PcCo}]$ or $[\text{H}_{16}\text{PcCo}]$ do not even complex 1-triphenyl-phosphoranylidene-2-propanone.

The aromatic 1-triphenylphosphoranylidene-2-propanone is relatively stable and a valuable chemical reagent. Aliphatic, electron-rich, 1-trialkylphosphoranylidene-2-propanones, on the other hand, are not used extensively.^[18] Indeed, only the methyl, ethyl, and butyl derivatives are reported.^[19] Their preparation can be accomplished by the stoichiometric acetylation of phosphorus ylides, $\text{R}_3\text{P}=\text{CH}_2$, with an acetyl metal complex, or acetyl chloride. The latter reagent, however, yields the diacetyl derivative as well. The products are unstable and decompose with the production of phosphane oxides.^[19] The lack of applications and stability notwithstanding, we have explored the oxidative formation of 1-tributylphosphoranylidene-2-propanones by treating acetone with the corresponding phosphane, Bu_3P . The same blue to purple color change, as observed in the reaction with Ph_3P , occurs in the visible region. The UV/Vis spectra of the product derived from Bu_3P is virtually identical to that of the product from the reaction with Ph_3P , which suggests that the corresponding complex, $[\text{F}_{64}\text{PcCo}(\text{1-tributylphosphoranylidene-2-propanone})_2]$ (**3**) forms in solution. Isolation of **3** or the phosphorane under ambient conditions, however, leads to partial decomposition, but both can be detected by mass spectrometry. Optimization of this reaction was not pursued because of its limited utility.

The combination of the nonplanar biconcave nature of the phthalocyanine, the type of metal (redox or non-redox) and the strong electron-withdrawing effects of the fluorine groups, appears to be critical for reactivity. In addition, the fluorinated pockets of the phthalocyanine complexes appear to both stabilize and promote the coupling reaction of the coordinated acetone molecules.

Noteworthy is that ylides, useful Wittig reagents, are generally prepared by a different route.^[20–22] Starting with a molecule with C–H groups, RCH_3 , a halogenated derivative, RCH_2X , is formed by the reaction with a halogen. Next, the carbon–phosphorus bonds are formed [Eqs. (2), (3)].



B^-M^+ is a metal hydroxide (in aqueous environments) or *n*-butyl lithium (in non-aqueous environments). To form the ylide, two hydrogen atoms of a substrate are removed by halogen atoms, which do not become part of the product. Our observations indicate that these hydrogen atoms could be removed catalytically as water, with no need for halogen

atoms, by using air at ambient conditions [Equation 1]. This type of carbon–phosphorus coupling extends the classical synthesis of Wittig reagents.

In summary, we report the facile preparation of the first representative of a novel class of robust homogeneous catalysts. This material resembles an enzyme because of the presence of a heme-like metal center buried inside a sterically restricting, but robust cavity that, as shown above, is essential for catalysis. The enzyme-like complex can couple phosphanes with acetone to produce ylides and water at ambient conditions, by using air (as opposed to halogenated chemicals) as the sole reagent. This chemistry might afford the replacement of the classical stoichiometric keto–ylide formation reaction by a catalytic process.

Work aimed at elucidating the mechanistic details and extending both this catalyst class and the scope of the oxidation chemistry to other substrates is in progress.

Experimental Section

1: A mixture of perfluoro-(4,5-di-isopropyl)phthalonitrile,^[4] (2.253 g, 4.505 mmol) and cobalt(II) acetate, (0.199 g, 1.123 mmol) was heated under argon to 230 °C for 100 min. The color changed to deep green. After cooling, the mixture was purified by chromatography on silica gel using 10 % acetone/pentane to give **1** in 34.5 % yield. M.p. > 300 °C; MS (FAB, NBA): 2057 [M^+]; UV/Vis (acetone) λ_{max} [nm] (log ϵ): 326 (4.13), 366 (3.91), 652 (3.90), 668 (4.05); FT-IR (NaCl, cm^{-1}): $\tilde{\nu}_{\text{CO}}$ = 1698; 1524 (w), 1456 (w), 1287 (s), 1250 (s), 1214 (s), 1168 (s), 1155 (s), 1109 (s), 1097 (s), 975 (w), 959 (w), 723 (s). The ESR spectrum exhibits the expected^[23] multiline pattern for a Co^{II} center with a singly-occupied d_z orbital: $g_{\parallel}$ = 2.008, $g_{\perp}$ = 2.217.^[24] The sample submitted for microanalysis was recrystallized from methanol, elemental analysis: calcd (%) for $\text{CoC}_{58}\text{H}_{38}\text{N}_8\text{O}_2\text{F}_{64}$, ($\text{CoC}_{56}\text{N}_8\text{F}_{64} \cdot 2$ methanol): C 32.80, H 0.38, N 5.28; found: C 32.52, H 0.56, N 5.27.

2: Excess triphenylphosphane was added to **1** (0.016 g, 0.0074 mmol) in acetone (10 mL). After 5 min, thin-layer chromatography (TLC), UV/Vis and IR spectroscopy indicated that the reaction was complete. No unreacted **1** was observed. UV/Vis (acetone) λ_{max} [nm] (log ϵ): 330 (4.88), 422 (4.50), 476 (4.42), 582 (4.60), 710 (4.74); FT-IR (NaCl, cm^{-1}): $\tilde{\nu}_{\text{CO}}$ = 1509 (s); 1436 (s), 1405 (s), 1250 (s), 1213 (w), 1166 (w), 1111 (w), 974 (w), 956 (w), 751 (s), 722 (s), 694 (s), 541 (s); ^{31}P NMR (121.495 MHz, $[\text{D}_6]\text{acetone}$, H_3PO_4) δ = 15.53 (for the uncoordinated ylide). Elemental analysis: calcd (%) for $\text{CoC}_{98}\text{H}_{38}\text{N}_8\text{O}_2\text{F}_{64}\text{P}_2$: C 43.66, H 1.42, N 4.16; found: C 43.51, H 1.41, N 4.29. X-ray quality crystals were grown by the slow evaporation of the solution in air. About 10 % triphenylphosphane oxide (relative to the ylide) was produced along with **2** in a parallel reaction, consistent with the observations that triphenylphosphane oxide is produced in toluene from Ph_3P and air in the presence of acetone-depleted $[\text{F}_{64}\text{PcCo}]$. Triphenylphosphane oxide does not react separately with acetone in the absence or presence of $[\text{F}_{64}\text{PcCo}]$, and thus it is not an intermediate on the reaction path to 1-triphenylphosphoranylidene-2-propanone.

3: A 200-fold excess of tributylphosphane, (0.5 mL, 2.007 mmol) was added to **1** (0.020 g) in acetone (50 mL). A purple color developed immediately. UV/Vis (acetone) λ_{max} [nm] (log ϵ): 340 (4.77), 426 (4.48), 474 (4.45), 578 (4.62), 710 (4.76); MS (FAB, NBA): 2577 [$M+1$]. Addition of excess acetone to **3** resulted in the regeneration of **1** in quantitative yield, as judged by UV/Vis spectroscopy, and free 1-tributylphosphoranylidene-2-propanone. GC-MS: 257 [M^+].

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Observation of Uniaxial Negative Thermal Expansion in an Organic Crystal**

Henrik Birkedal,* Dieter Schwarzenbach, and Philip Pattison

In the past few years, crystal engineering has attracted ever-increasing interest.^[1] This subject is concerned with the design of solids with specific, controlled properties. One such coveted property is negative thermal expansion (NTE). Several inorganic systems exhibiting NTE are known^[2–4] but organic materials displaying NTE have very rarely been reported.^[5] Here we show that the monohydrate of the dipeptide tryptophylglycine^[6] (TrpGly · H₂O) crystallizes in a supramolecular helix that extends throughout the entire crystal, thus forming a peptide nanotube,^[7] and that the thermal expansion along the helical axis is negative below room temperature.

The crystal structure of TrpGly · H₂O was investigated at 295 and 120 K using bending magnet synchrotron radiation at the Swiss–Norwegian Beam Line (SNBL at ESRF, France).^[8] The single-crystal sample had dimensions 20 × 30 × 180 μm³. In spite of the small size, data of high quality could be collected and refinements proceeded to an $R_1(\text{all})$ below 3.2 % at both temperatures. The molecular structure is shown in Figure 1.

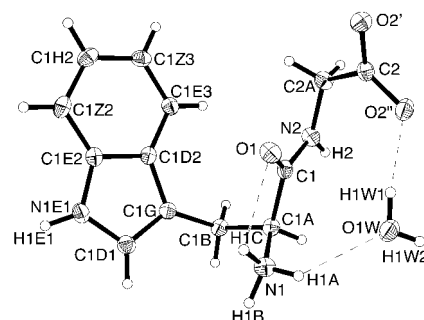


Figure 1. Structure of TrpGly · H₂O as determined at 120 K. Displacement ellipsoids are drawn at the 50 % probability level. Only the majority water site is shown. Hydrogen atoms involved in conventional hydrogen bonds are labeled. Dashed lines indicate hydrogen bonds.

The crystal structure is tetragonal and the peptide forms a helical structure parallel to the c axis. This helix, Figure 2, encloses a channel in which the water molecules are located. The peptide channel extends throughout the entire crystal and has approximate internal dimensions of 8.3×8.3 Å². The van der Waals accessible volume^[9] is 80.5 and 76.8 Å³ per unit cell at 295 and 120 K, respectively. The peptide helix thus forms a peptide nanotube occupied by water molecules. The

[*] Dr. H. Birkedal, Prof. D. Schwarzenbach, Dr. P. Pattison
Institute of Crystallography
University of Lausanne
BSP Dorigny, 1015 Lausanne (Switzerland)
Fax: (+41) 21-692-3605
E-mail: Henrik.Birkedal@ic.unil.ch

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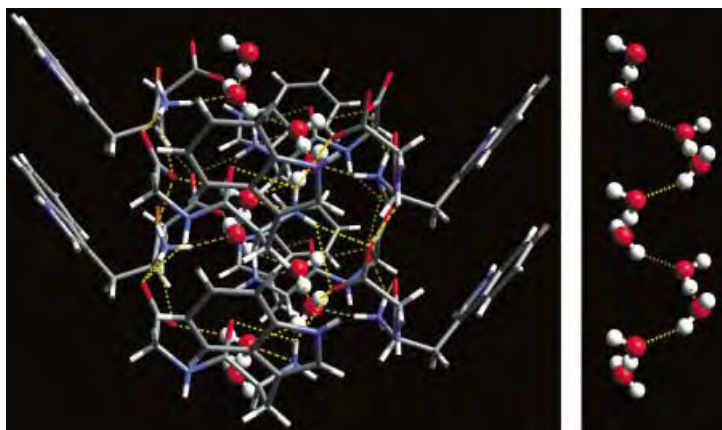


Figure 2. Supramolecular peptide helix parallel to the crystallographic c axis. Left: peptide helix enclosing the water helix. Right: water helix. Only the majority water site is shown.

water molecules are disordered at both temperatures. There is one majority site, shown in Figures 1 and 2, and several minor sites distributed in the channel. The minor sites all have slightly less favorable hydrogen-bond geometries than the majority site, which is connected to the peptide framework by a hydrogen bond. The occupation of the majority site, O1W, increases from 0.578(9) at 295 K to 0.693(11) at 120 K. The data were of sufficient quality to allow refining of the positions of all hydrogen atoms bound to hydrogen-bond donors. The strongest hydrogen bond in the structure is the charge assisted, three-center, $-N-H^+ \cdots -OOC-$, intermolecular hydrogen bond involving H1B (Figure 1). In line with the strength of this interaction, the N1–H1B bond is significantly longer than the other NH_3 bonds. Even more interesting, the hydrogen atom on the indole nitrogen atom of tryptophane is displaced out of the indole plane. Thereby a more linear, and hence stronger, hydrogen bond is formed.^[10] This observation reflects the importance of refining hydrogen positions when high quality X-ray data are available.

The crystal structure of TrpGly·H₂O was recently determined independently of our investigation by using room temperature laboratory X-ray data on a crystal measuring $440 \times 120 \times 20 \mu\text{m}^3$.^[11] The microcrystal data presented here are of far better quality and provide much more detailed information on the structure.

The single-crystal data showed that the c lattice parameter expands when lowering the temperature. To investigate this unusual behavior, we undertook a study of the thermal expansion by powder diffraction using the MAR345 imaging plate at SNBL as the detector.^[12] This approach allows for very rapid data collection^[13] as a function of temperature. In the present case, 25 powder diagrams were measured between 270 and 120 K in only 75 min. The resulting temperature dependence of the lattice parameters is plotted in Figure 3. The thermal expansion along the c axis is negative in the entire range, but of much smaller absolute magnitude than that along the a axis. Therefore, the volume thermal expansion is positive. The data were fitted by Equation (1). The coefficients of thermal expansion thus obtained are

$$p(T) = p_0(1 + \alpha_p T(1 + \alpha'_p T)) \quad (1)$$

$a_0 = 15.932(2) \text{ \AA}$, $\alpha_a = 2.92(12) \times 10^{-5} \text{ K}^{-1}$, $\alpha'_a = 1.2(2) \times 10^{-3} \text{ K}^{-1}$, $c_0 = 5.2104(5)$, $\alpha_c = -0.106(10) \times 10^{-5} \text{ K}^{-1}$, and $\alpha'_c = -1.92(7) \times 10^{-3} \text{ K}^{-1}$. We propose that the water ordering is linked with the NTE. When the temperature is lowered, the enthalpy gain of water ordering starts to dominate the free energy and the occupancy of the favored major site increases. The increased localization of water molecules in the major site leads to an enhanced correlation along the c axis which in turn requires more space and results in NTE. This model is akin to the explanation of the expansion of ice relative to water. In this picture, it can be expected that when and if the water orders completely, the thermal expansion along the c axis will change sign. We are presently undertaking very low temperature diffraction studies to confirm this theory.

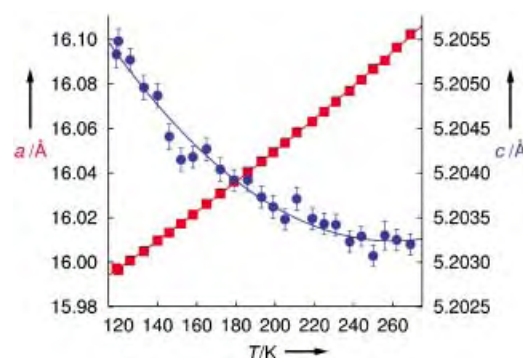


Figure 3. Temperature dependence of the independent tetragonal lattice parameters, a (red) and c (blue). Note the negative thermal expansion of the c axis.

In summary, we have shown that the crystal structure of TrpGly·H₂O consists of peptide nanotubes. These tubes contain water molecules, which gradually order upon lowering the temperature. This ordering is accompanied by negative thermal expansion along the tube axis. This study demonstrates how the combination of high quality single-crystal and powder diffraction data can provide valuable insight into the physical properties of materials. The use of synchrotron radiation greatly facilitates these studies and increases the attainable precision.

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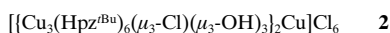
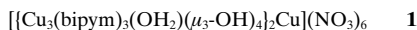
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Supramolecular Templating of the Double-Cubane $[\{\text{Cu}_3(\text{Hpz}^{\text{tBu}})_6(\mu_3\text{-Cl})(\mu_3\text{-OH})_3\}_2\text{Cu}]\text{Cl}_6$ ($\text{Hpz}^{\text{tBu}} = 5\text{-tert-Butylpyrazole}$)**

Xiaoming Liu, Judith A. McAllister, Marcelo P. de Miranda, Benjamin J. Whitaker, Colin A. Kilner, Mark Thornton-Pett, and Malcolm A. Halcrow*

While the $[\text{M}_4(\mu_3\text{-X})_4]^{4+}$ ($\text{M} = \text{transition ion}$, $\text{X} = \text{anion or dianion}$) cubane structure is a common motif in transition metal chemistry and biochemistry, only a few examples of vertex-sharing double-cubane compounds are known.^[1–8] We note in particular **1** (bipym = 2,2'-bipyrimidine), which is the only compound with this topology whose magnetochemical properties have been fully elucidated to date.^[5] We report here a new example of a heptacopper double-cubane complex, **2**, whose molecular structure and magnetochemistry differ substantially from those of **1**. Moreover, the unusual structure of **2** is supported by a unique pattern of supramolecular cation:anion interactions.



Turquoise crystals of $\mathbf{2} \cdot 2\text{CH}_2\text{Cl}_2$ were grown from CH_2Cl_2 /pentane mixtures.^[9] The asymmetric unit of these crystals contains half a complex molecule with Cu(1) lying on a crystallographic inversion center, forming a $[\{\text{Cu}_3(\text{Hpz}^{\text{tBu}})_6(\mu_3\text{-Cl})(\mu_3\text{-OH})_3\}_2\text{Cu}]^{6+}$ double-cubane (Figure 1). The shared-vertex Cu(1) is ligated by six OH^- ligands, with an axis of Jahn–Teller elongation along the $\text{O}(7)\text{-Cu}(1)\text{-O}(7')$ vector. The other Cu ions exhibit tetragonal geometries, with two OH^- and two Hpz^{tBu} ligands in the basal plane and axial contacts to two Cl^- ions. Cu(3) and Cu(4) adopt almost identical geometries, with contacts of 2.7949(5)–2.9129(6) Å to Cl(62) and one other Cl^- ligand. However, Cu(2) has a shorter distance of 2.5502(5) Å to Cl(62), and a much longer distance of 3.7433(6) Å to Cl(63) (not shown in Figure 1).

In addition to Cl(62) and its symmetry-generated equivalent, there are six Cl^- ions disposed in a ring around the heptacopper core of the molecule (Figure 2). Each of these Cl^- ions accepts three hydrogen bonds, from one OH^- and two Hpz^{tBu} N–H donors. Cl(64) and Cl(65) are in near-

[*] Dr. M. A. Halcrow, Dr. X. Liu, Dr. M. P. de Miranda, Dr. B. J. Whitaker, C. A. Kilner, Dr. M. Thornton-Pett
School of Chemistry
University of Leeds
Leeds LS2 9JT (UK)
Fax: (+44) 113-233-6565
E-mail: M.A.Halcrow@chem.leeds.ac.uk

Dr. J. A. McAllister
Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge CB2 1EW (UK)
and
Interdisciplinary Research Centre in Superconductivity
University of Cambridge
Madingley Road, Cambridge CB3 0HE (UK)

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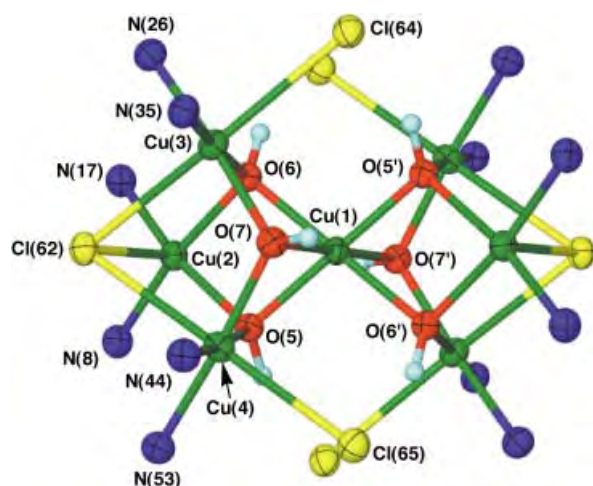


Figure 1. View of the $[\text{Cu}_3(\text{Hpz}^{\text{tBu}})_6(\mu_3\text{-Cl})(\mu_3\text{-OH})_3]_2\text{Cu}^{6+}$ core in the crystal structure of **2** · 2 CH_2Cl_2 . For clarity, only the coordinated N atoms of the Hpz^{tBu} ligands are shown. Thermal ellipsoids are at the 50% probability level. Color code: Cu: green; O: red; N: blue; Cl: yellow; H: turquoise. Selected bond lengths [Å] and angles [°]: Cu(1)–O(5) 1.9781(13), Cu(1)–O(6) 1.9675(13), Cu(1)–O(7) 2.2957(13), Cu(2)–O(5) 1.9731(14), Cu(2)–O(6) 1.9862(13), Cu(3)–O(6) 1.9940(13), Cu(3)–O(7) 1.9549(14), Cu(4)–O(5) 2.0076(14), Cu(4)–O(7) 1.9493(13); O(5)–Cu(1)–O(6) 81.00(5), O(5)–Cu(1)–O(7) 99.00(5), O(5)–Cu(1)–O(7) 75.74(5), O(5)–Cu(1)–O(7) 104.26(5), O(6)–Cu(1)–O(7) 76.06(5), O(6)–Cu(1)–O(7) 103.94(5), O(5)–Cu(2)–O(6) 80.66(6), O(6)–Cu(3)–O(7) 83.86(6), O(5)–Cu(4)–O(7) 83.51(6), Cu(1)–O(5)–Cu(2) 96.61(6), Cu(1)–O(5)–Cu(4) 102.33(6), Cu(2)–O(5)–Cu(4) 108.97(6), Cu(1)–O(6)–Cu(2) 96.53(6), Cu(1)–O(6)–Cu(3) 101.59(6), Cu(2)–O(6)–Cu(3) 111.11(6), Cu(1)–O(7)–Cu(3) 92.12(5), Cu(1)–O(7)–Cu(4) 93.65(5), Cu(3)–O(7)–Cu(4) 118.55(7). Primed atoms are related to unprimed atoms by the symmetry operation: $1-x, 1-y, 1-z$.

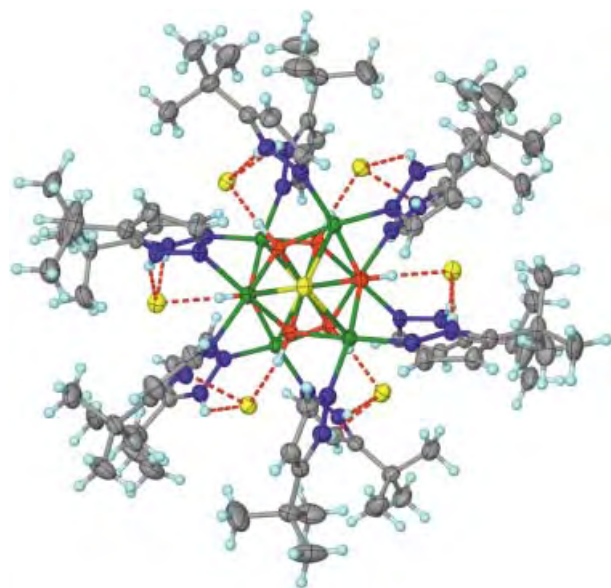


Figure 2. View of the $[\text{Cu}_3(\text{Hpz}^{\text{tBu}})_6(\mu_3\text{-Cl})(\mu_3\text{-OH})_3]_2\text{CuCl}_6$ molecule in the crystal structure of **2** · 2 CH_2Cl_2 , showing the hydrogen-bonding interactions to the Cl^- ions. The view is parallel to the $\text{Cl}(62) \cdots \text{Cu}(1) \cdots \text{Cl}(62')$ vector in Figure 1. Color code as for Figure 1 with C: gray.

identical environments 2.8–2.9 Å from the closest Cu ion (see above). However Cl(63), which is hydrogen-bonded to the OH^- ligand O(7') lying on the axis of Jahn–Teller elongation at Cu(1), is displaced from the equivalent site by 0.9 Å away from Cu(2). These hydrogen-bonded Cl^- ions are encapsu-

lated inside the Hpz^{tBu} *tert*-butyl substituents, which enclose the molecule in a hydrophobic sheath.

Magnetic susceptibility data were obtained between 5–330 K from a powder sample of **2**, in an applied field of 2000 G (Figure 3). At 300 K $\chi_{\text{M}}T = 2.4 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$, which is

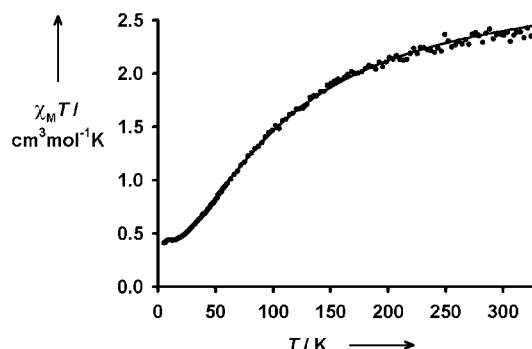
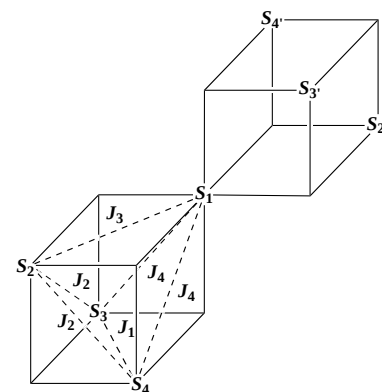


Figure 3. Plot of $\chi_{\text{M}}T$ versus T for a powder sample of **2** (circles), showing the best theoretical fit (line). See text for fitting details.

slightly smaller than the spin-only value expected for seven noninteracting $S = 1/2$ Cu^{II} ions ($2.6 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$).^[10] As the temperature is lowered $\chi_{\text{M}}T$ decreases, reaching a plateau of $0.44 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$ at 15 K which is consistent with a fully populated $S = 1/2$ ground state.^[10] These data were interpreted by using the Hamiltonian in Equation (1) (see Scheme 1 for the exchange-coupling scheme adopted).^[11]

$$H = -2J_1(S_3S_4 + S_3S_4) - 2J_2(S_2S_3 + S_2S_4 + S_2S_3 + S_2S_4) - 2J_3(S_1S_2 + S_1S_2) - 2J_4(S_1S_3 + S_1S_4 + S_1S_3 + S_1S_4) \quad (1)$$

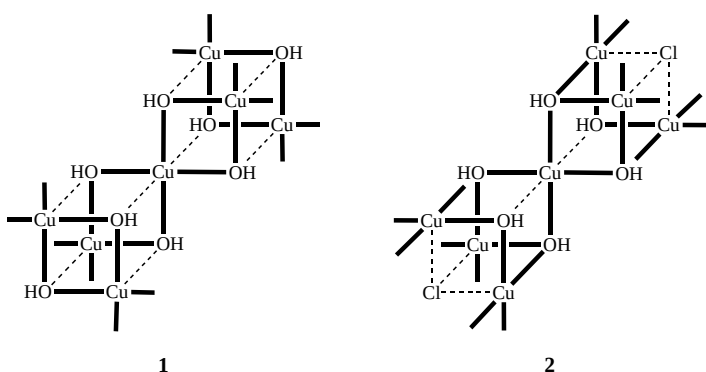


Scheme 1. Exchange-coupling scheme employed to analyze the magnetic data of **2**. Each spin equates to the correspondingly numbered Cu ion in Figure 1 (i.e. $S_1 \equiv \text{Cu}(1)$ etc.).

During the analysis it was found that $J_2 \approx J_4$, and that both of these parameters were poorly defined owing to correlation problems. Therefore, these two J values were constrained to be equal for the final fitting, which yielded $g = 2.14$, $J_1 = -72$, $J_3 = -21$ and $J_2 = J_4 = -16 \text{ cm}^{-1}$ (Figure 3). The constant J_3 describes superexchange mediated by two OH^- ligands that both lie in the xy magnetic planes of Cu(1) and Cu(2). The observed value for this coupling agrees well with Haase's

correlation for basal–basal superexchange in $[\text{Cu}_4(\mu_3\text{-OR})_4]^{4+}$ (R = alkyl) cubanes, which predicts $J_3 \approx -30 \text{ cm}^{-1}$ for the observed average Cu(1)–O–Cu(2) angle of $96.57(8)^\circ$.^[12] The other superexchange constants J_1 , J_2 , and J_4 in **2** are all effectively mediated by $[\text{Cu}_2(\mu\text{-OH})]^{3+}$ bridges, across average Cu–O–Cu angles of $118.55(7)^\circ$, $110.04(8)^\circ$, and $101.96(8)^\circ$, respectively. This is consistent with J_1 being more antiferromagnetic than J_2 or J_4 .^[12, 13] Since J_1 is the strongest antiferromagnetic coupling in the molecule, this means that Cu(1), Cu(2), and Cu(2') are spin-frustrated with respect to Cu(3), Cu(4), Cu(3'), and Cu(4').

While they both have C_s symmetry, the heptacopper cores of **1**^[5] and **2** are very different (Scheme 2). Compound **1** can be described structurally and magnetically as a pair of vertex-linked C_2 -symmetric $[\text{Cu}_4(\text{bipy})_3(\mu_3\text{-OH})_4]^{4+}$ cubanes. This



Scheme 2. Comparative molecular structures of **1** and **2**, showing the basal (thick lines) and apical (dashed lines) Cu–X (X = O, Cl) bonds.

“dimer of dimers” motif is common in $[\text{Cu}_4(\mu_3\text{-OR})_4]^{4+}$ (R = H, alkyl) cubane compounds.^[12, 14] However, the individual $[\text{Cu}_4(\text{Hpz}^{\text{Bu}})_6(\mu_3\text{-Cl})(\mu_3\text{-OH})_3]^{4+}$ cubane moieties in **2** are C_s -symmetric, being distorted from C_{3v} symmetry by the Jahn–Teller elongation at Cu(1). This is the first example of this structural type in Cu^{II} chemistry.

There is a small, but growing, number of compounds containing an enclosed guest anion or cation inside a polyoxometalate^[15] or polynuclear coordination complex^[16] cage. The guest ion in these compounds templates the structure of the surrounding framework, despite interacting with it only through electrostatic and van der Waals interactions. Compound **2** is an inversion of the usual scenario, in that the metal core is encapsulated by a belt of hydrogen-bonded, templating anions. Experiments are in progress to prepare new mono- and bidentate ligands designed as anion receptors, in order to use supramolecular chemistry to prepare other novel metal–oxo or –hydroxo cluster architectures.

Experimental Section

To a mixture of CuCl_2 (0.13 g, 1.0 mmol) in MeOH (30 mL) was added a MeOH (20 mL) solution of NaOH (0.040 g, 1.0 mmol) and 3[5]-*tert*-butylpyrazole (0.24 g, 2.0 mmol). The resultant dark green solution was stirred at 293 K for three days, then evaporated to dryness. Extraction of the residue with CH_2Cl_2 , and layering of the resultant green solution with

pentane, yielded turquoise crystals of **2**. Yield 0.18 g, 54% based on Cu. Elemental analysis calcd (%) for $\text{C}_{84}\text{H}_{150}\text{Cl}_8\text{Cu}_7\text{N}_{24}\text{O}_6$: C 43.47, H 6.51, N 14.49; found: C 43.50, H 6.55, N 14.55.

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Proof of Principle in the Selective Treatment of Cancer by Antibody-Directed Enzyme Prodrug Therapy: The Development of a Highly Potent Prodrug**

Lutz F. Tietze,* Tim Feuerstein, Anja Fecher, Frank Haunert, Olaf Panknin, Ulrich Borchers, Ingrid Schuberth, and Frauke Alves

The antibody-directed enzyme prodrug therapy (ADEPT),^[1] first described by Bagshawe,^[2] is a new strategy for a selective treatment of cancer, in which a nontoxic prodrug is enzymatically converted into a cytotoxic compound selectively at the surface of malignant cells by employing an enzyme-immuno conjugate. As a proposed requirement for the prodrug the corresponding cytotoxic compound should possess an $IC_{50} < 10 \text{ nM}$ ^[3] (IC_{50} : drug concentration required for 50% inhibition of target cells) and the quotient of the IC_{50} of the prodrug and the prodrug in the presence of the related enzyme (QIC_{50}) should be above 1000.^[4]

Because of its high cytotoxicity with an IC_{50} of about 0.03 nM (cell line L1210) the antibiotic CC-1065 (**1**), which was isolated from *Streptomyces zelensis*, is a good target.^[5] It contains a spirocyclopropyl moiety which can alkylate N3 of adenine in AT-rich parts of the minor groove of DNA. Synthetically, the spirocyclopropyl moiety may be formed from a chloromethyl group, and such seco-compounds are also found in nature as duocarmycin SA.^[6] It is assumed that the seco-compounds are first transformed into the spirocyclopropyl derivatives which then react with an adenine group in the DNA. We have shown that such seco-compounds may reversibly be detoxified by glycosylation of the phenolic hydroxyl group which prohibits the formation of the spirocyclopropyl group.^[7]

However, the seco-CBI galactoside **2**, which by enzymatic cleavage leads to CBI **4** (Figure 1), a potent analogue of CC-1065 developed by Boger et al.^[8], shows a rather high cytotoxicity with a low QIC_{50} of 32; this may be explained by a direct alkylation of an adenine group by the chloromethyl group in the protected seco-compound **2**.^[4]

Here we describe the synthesis as well as the in vitro and in vivo investigations using an enzyme-immuno conjugate of the seco-CBI-Q-galactoside **3** (Figure 1), which shows excellent results. It is important to note that compound **3**, which in the presence of β -D-galactosidase leads to the highly cytotoxic CBI **4**, contains a secondary chloride moiety instead of a

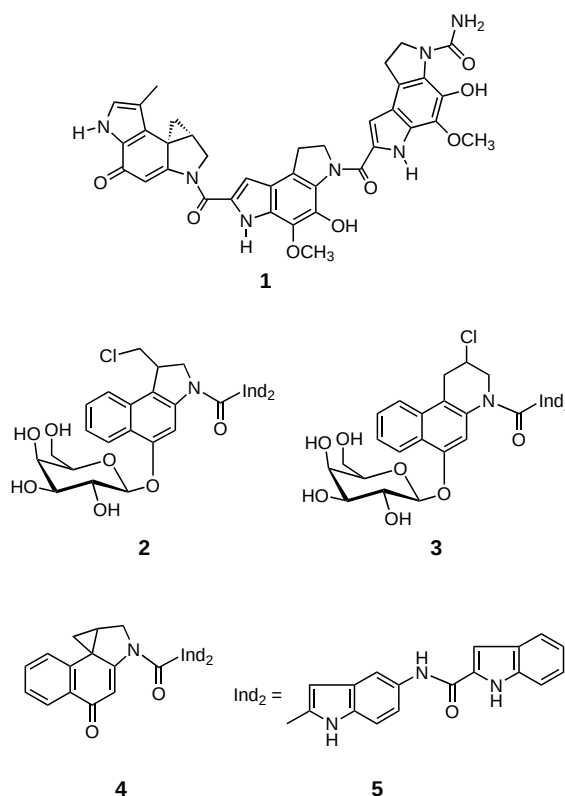


Figure 1. CC-1065 (**1**), seco-CBI-galactoside **2**, seco-CBI-Q-galactoside **3**, and CBI **4**.

primary as in **2** suggesting that the direct alkylation should be diminished by steric hindrance.^[9]

Starting from the known racemic alcohol **6** (Figure 2), the silyl ether is synthesized by protection of the secondary hydroxyl group with *tert*-butyldiphenylsilylchloride (TBDPSCI). Hydrogenolytic cleavage of the benzylic ether in **7**, treatment of the obtained phenol using the Schmidt procedure^[10] with the trichloroacetimidate of tetraacetylgalactose **8** in the presence of $BF_3 \cdot Et_2O$ followed by addition of bisindolylcarboxylic acid^[11] and 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide (EDC) in an one pot procedure yields **9** in 38% overall yield. Deprotection of the secondary alcohol and substitution of the hydroxyl group by chloride using the Appel procedure^[12] with triphenylphosphane in tetrachloromethane and acetonitrile for 5 h at 40 °C leads to **10**. Finally, solvolysis of the acetyl groups using sodium methoxide in methanol completes the synthesis to give **3** as a 1:1 mixture of two diastereomers in 17% yield over three steps.

The cytotoxicity of the prodrug **3** in the absence and presence of β -D-galactosidase was determined in a cellular cytotoxicity assay by exposure to the human bronchial carcinoma cell line A549 and the human pancreatic ductal adenocarcinoma cell line PancTu 1 for 24 h;^[4, 7] As expected, the cytotoxicity of **3** in the presence of β -D-galactosidase with an $IC_{50} = 0.20 \text{ nM}$ (A549) and an $IC_{50} = 0.13 \text{ nM}$ (PancTu1) is very high. In contrast, the prodrug **3** in the absence of β -D-galactosidase is less toxic by a factor of 1600 for the cell line A549 and by a factor of 3140 for the cell line PancTu1 (Figure 3).

[*] Prof. Dr. Dr. h.c. L. F. Tietze, Dipl.-Chem. T. Feuerstein, Dr. A. Fecher, Dipl.-Chem. F. Haunert, Dipl.-Chem. O. Panknin, Dr. U. Borchers, Dr. I. Schuberth
Institut für Organische Chemie
der Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-399476
E-mail: ltietze@gwdg.de

Dr. F. Alves
Zentrum Innere Medizin, Hämatologie und Onkologie
Georg-August-Universität Göttingen

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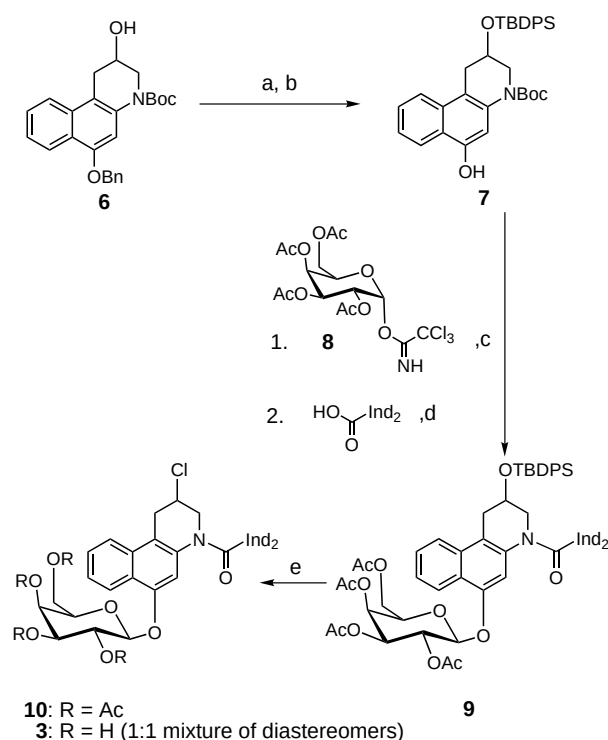


Figure 2. Synthesis of seco-CBI-Q-galactoside **3**: a) TBDPSCI, imidazol, DMF, RT, 3 days, 94 %; b) Pd/C, $\text{NH}_4\text{CO}_2\text{H}$, acetone, reflux, 1 h, 99 %; c) **8**, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , $-10^\circ\text{C} \rightarrow \text{RT}$, 5 h; d) EDC, DMF, RT, 15 h, 41 % over two steps; e) 1. TBAF $\cdot$ SiO_2 , THF, 6 h, 47 %, 2. Ph_3P , CCl_4 : CH_3CN 1:1, 40°C , 5 h, 38 %, 3. NaOMe, MeOH, RT, 30 min, 95 %. Boc = *tert*-butoxycarbonyl, TBAF = tetrabutylammonium fluoride.

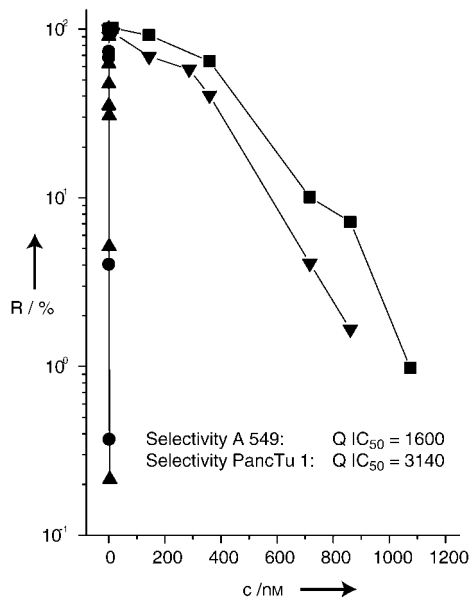


Figure 3. In vitro cytotoxicity of **3** against human bronchial carcinoma cells of line A549 and human pancreatic ductal adenocarcinoma cells of line PancTu 1. (▼): Cytotoxicity of **3** against A549. (●): Cytotoxicity of **3** against A549 in the presence of β -D-galactosidase (*Escherichia coli*, 0.4 U mL^{-1}). (■): Cytotoxicity of **3** against PancTu 1. (▲): Cytotoxicity of **3** against PancTu 1 in the presence of β -D-galactosidase (*Escherichia coli*, 0.4 U mL^{-1}). Cells were exposed to various concentrations of the test substance for 24 h at 37°C ; after 12 days of incubation clone formation was compared to untreated control assay and the relative clone-forming rate was determined; R = relative colony-forming rate, c = concentration.

The acute toxicity of seco-CBI-Q-galactoside **3** was evaluated by administration to young male and female SCID mice using DMSO:0.9 % saline solution (1:200) as vehicle.^[13] Each animal received either a single dose (group 1), or three (group 2), or five doses (group 3), respectively, on successive days with each dose containing $20 \mu\text{g kg}^{-1}$ of **3**. Control animals (group 4) received five intraperitoneal (i.p.) doses of vehicle solution, equivalent to the volume of the test solutions administered.

All the animals tolerated the treatment well without any complications, such as, body weight loss or apathetic behavior. In all organs examined (e.g. lung, liver, spleen, kidneys) no macroscopical or microscopical changes could be detected by histological examination. Thus, the study shows that the prodrug **3** is nontoxic to normal organs and blood parameters of SCID mice using therapeutic doses; this indicates that **3** is not converted into **4** by enzymes expressed by the SCID mice. This is a necessary prerequisite for application within ADEPT.

To evaluate the potency of prodrug **3** for an in vivo application, orthotopic tumors of the human bronchial carcinoma cell line A549 and the pancreatic ductal adenocarcinoma cell line PancTu 1 in SCID mice were generated.^[14] The treatment started on day eight after orthotopic implantation by intravenous (i.v.) administration of the immunoconjugate of galactosidase and a human epithelial monoclonal antibody. After a clearance time of 84 h^[15] the galactoside **3** ($25 \mu\text{g kg}^{-1}$, using DMSO:0.9 % saline solution (1:200) as vehicle) was applied i.p. to the mice and given every second day until sacrifice on day 30. Primary tumor volume in treated mice was significantly decreased whereas tumor invasion in the control animals caused complications such as acute dyspnoea and weight loss (Figure 4).



Figure 4. Macroscopic appearance of tumors: A) Lung tumor in a treated mouse. B) Lung tumor in a control mouse.

Histological examination of lung tissue shows that in treated animals the tumor is only located in small areas (Figure 5). In contrast, the lung tumor in controls invades the whole lung.

In conclusion, with the galactoside **3** we have developed a new highly potent prodrug, which meets all the necessary requirements for a successful use in ADEPT: excellent selectivity ($\text{Q IC}_{50} = 1600$ and 3140 for the used cell lines), low systemic toxicity and high cytotoxicity of the corresponding drug ($\text{IC}_{50} = 0.20$ and 0.13 nM , respectively). In addition, first preclinical investigations on mice show promising results. A further advantage of this compound is its reasonable water

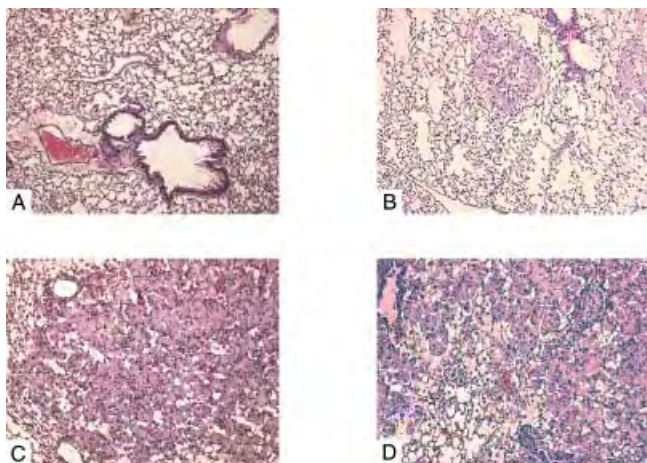


Figure 5. Histological characteristics of the lung tumors: The tumor tissue shows prominently roundly formed nuclei and a solid structure; operatively expansive. A) and B) Haematoxylin and Eosin staining of lung tissue of a treated mouse; the tumor tissue is only located in small areas. C) and D) Haematoxylin and Eosin staining of lung tissue of a control mouse; tumor invading the bronchus.

solubility arising from its hydrophilic sugar moiety and the fact that it seems not to penetrate the cell membrane. Thus, cellular human galactosidase may be used for an activation. Finally, the synthesis allows the preparation of analogues containing different sugar moieties.

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Magnetization of Chiral Monolayers of Polypeptide: A Possible Source of Magnetism in Some Biological Membranes**

Itai Carmeli, Viera Skakalova, Ron Naaman,* and Zeev Vager

Some biological membranes are affected by weak magnetic fields.^[1] In particular, magnet-induced orientation was observed in the outer segments of retinal rods,^[2] chloroplasts,^[3] bacterial chromatophores,^[4] purple membranes,^[5] and recently in black lipid membranes.^[6] The membrane surfaces tend to align perpendicular to the magnetic field. Alignment due to anisotropic magnetic susceptibility,^[7] which explains alignment effects in liquid crystals, requires much higher magnetic fields than were used in the above experiments. Hence, no existing theory could explain these significant observations. The lack of physico-microscopic understanding of the effect of magnetic fields on biological membranes prevents the comprehension of its significance.

By studying well-characterized monolayers of polyaniline we were able not only to obtain results similar to those observed in biological membranes, but also to gain an insight into the details of a mechanism that may account for the previously observed magnetic behavior of membranes. We propose an explanation of these phenomena in terms of a physical model, the components of which are supported by the experimental results presented here.

Self-assembled monolayers of L- or D-polyalanine polypeptides in the form of α -helices were prepared on glass slides coated with a 100-nm thick annealed gold film. The orientation of the molecules was monitored by IR spectroscopy in the presence and absence of a magnetic field. In addition, we

[*] Prof. R. Naaman, I. Carmeli, Dr. V. Skakalova, Prof. Z. Vager
Department of Chemical Physics
Weizmann Institute of Science
Rehovot 76100 (Israel)
Fax: (+972) 8-9344123
E-mail: ron.naaman@weizmann.ac.il

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investigated the selectivity of the layers towards spin-polarized electron transmission.

Connecting a sulfide group at the C- or N-terminus of the peptide makes the dipole moment of the attached molecules point away from or towards the substrate. Three types of films were investigated: poly(L-alanine) and poly(D-alanine), both connected to the surface at the C-terminus (LC and DC, respectively), and poly(D-alanine) connected to the surface at the N-terminus (DN). Polypeptide lengths between 16 and 22 amino acid units were used. The structure of the films was determined by means of their FT-IR spectra.^[8] The handedness of the adsorbed films was verified by circular dichroism absorption, and their thickness was measured by ellipsometry. Atomic force microscopy (AFM) was also carried out. All the results reported here were obtained at room temperature from close-packed layers.

The IR spectra of LC and DC monolayers were measured at magnetic field strengths of 0, ± 900 , and ± 4500 G applied perpendicular to the layer. Henceforth, "N" indicates magnetic field lines starting at the North Pole and penetrating through the gold surface to the monolayer, and vice versa for "S". Figure 1 shows grazing-angle IR spectra obtained for the

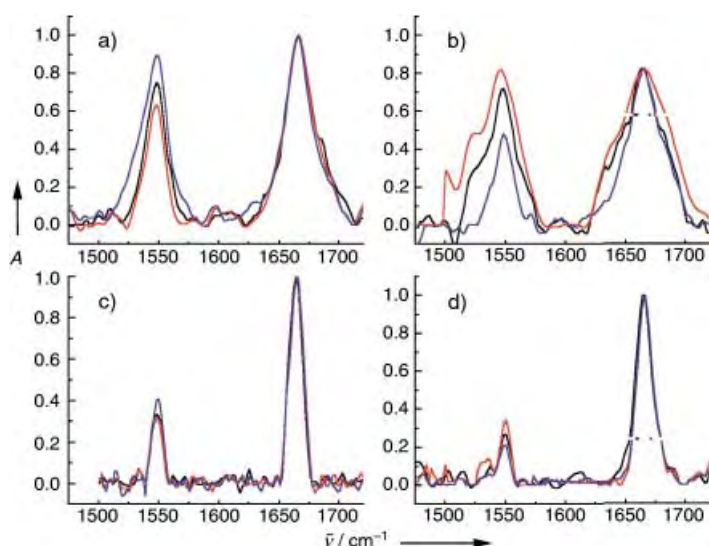


Figure 1. IR spectra of DC (a and c) and LC layers (b and d) showing the amide I (ca. 1665 cm^{-1}) and II bands (ca. 1550 cm^{-1}). The spectra are normalized to the peak of the 1665-cm^{-1} band. The spectra were recorded with S (red) or N magnets (blue) or without a magnetic field (black). The spectra in a and b were recorded at 4500 G , and those in c and d at 900 G . A = absorbance.

vibrations of the amido group.^[9] The amide I vibration is parallel to the molecular axis (at ca. 1665 cm^{-1}), while the amide II vibration at about 1550 cm^{-1} is perpendicular to the axis. The spectra are normalized to the peak of the 1665-cm^{-1} band. If the molecules are oriented normal to the surface, the intensity of the amide II component vanishes because the metal substrate cancels the transition dipole moment. Hence, the ratio between the intensity of the two peaks provides a direct measure of the tilt angle of the molecules relative to the surface normal.^[10]

From Figure 1 it is evident that the magnetic field affects the relative IR intensities. For the two LC layers (Figure 1b, d) S fields increase the average tilt angles, while N fields decrease them. The reverse is true for the DC layers (Figure 1a, c); that is, S fields decrease the average tilt angles, while N fields increase them. Larger fields lead to larger tilts. It takes 2–6 h for the effect of the magnetic field on the tilt angle to reach equilibrium. The time required depends on the strength of the magnetic field and on the quality of the monolayer, that is, its packing density and the average tilt angle. Denser layers require more time for equilibration in magnetic fields. The above magnetic-orientation effects within the layers provide clear evidence that the films have magnetic properties and that opposite magnetization occurs for opposite handedness. Classic magnetization of iron is interpreted as orientation of domains, and the magnetic orientation of these artificial LC and DC monolayers mimics orientational effects already found in biological membranes.^[5]

For the electron transmission studies, the samples were inserted into an ultrahigh vacuum chamber at $<10^{-8}\text{ mbar}$. Polarized photoelectrons were ejected from the substrate by applying a 248-nm laser beam with a $\lambda/4$ plate to create left- or right-handed circularly polarized light. Right-handed circularly polarized light induces positive helicity^[11] in the photoelectrons ejected from the gold substrate, and vice versa for left-handed polarized light. The photoelectrons are polarized by about 15%.^[12] After passing through the organic layers, energy distribution of the electrons was analyzed by a time-of-flight spectrometer.^[13]

Figure 2 presents the kinetic energy distributions of photoelectrons ejected with a left- or right-polarized laser. The spectra in panels a and c were obtained for the transmission of electrons through LC and DC films, and panel b for a DN film. Figures 2a and c confirm earlier results that showed a large asymmetry for the transmission of polarized electrons

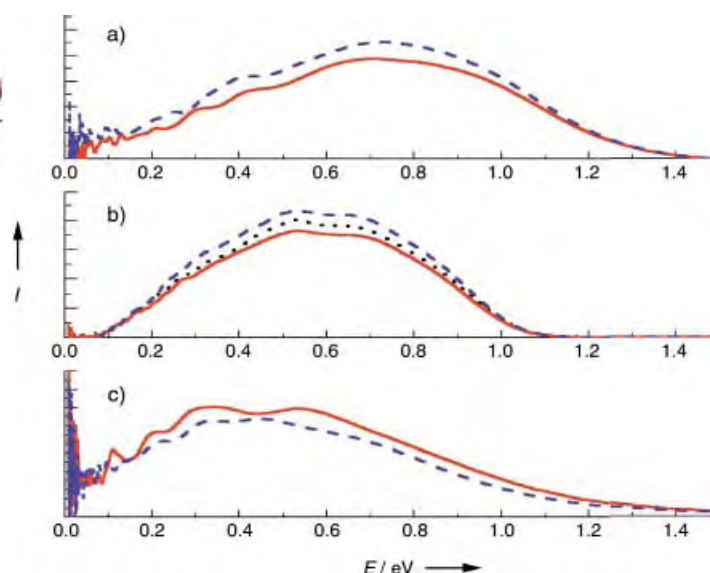


Figure 2. Energy distribution for photoelectrons ejected with a left (negative spin polarization; red, solid) or right circularly polarized laser (positive spin polarization; blue, dashed). The signal obtained with a linearly polarized laser is shown as a dotted black line. The electrons were transmitted through LC (a), DC (b), and DN films (c). I = intensity.

through organized films of chiral molecules.^[14] The sign of the asymmetry depends on the handedness of the molecules. Surprisingly, for a given handedness of the molecules the sign of the asymmetry switches upon reversing the way the molecules are adsorbed on the surface (from N- to C-bound molecules). This is clearly seen in Figures 2b and c. The observed asymmetry^[15] in the transmission through the layer of photoelectrons produced by left and right circularly polarized photons changes from 0.09 ± 0.02 to -0.10 ± 0.02 (Figures 2b and 2c, respectively). Importantly, the observed effect of 10 % is induced by a mere 15 % polarization of the photoelectrons.^[12] Thus, the selectivity for the incoming helicity of the electrons is as high as 70 %, and considering experimental error could be even higher.

Several questions arise from the above observations.

- Why are the layers magnetic?
- Why is there a relation between the direction of magnetism and the handedness of the molecules?
- Why is there a large spin selectivity for electron transmission?
- Why does it change sign with both change of handedness and change in the direction of the molecular electric dipole?

Before introducing a possible model for answering the above questions, a few remarks on some known physics of the observed phenomena are appropriate. In solution polyaniline molecules have a large electric dipole moment of about 50 D.^[16, 17] When the molecules are attached as a monolayer, they must lose most of their dipole moment; otherwise the repulsion between them would prevent close packing. Simple electrostatic arguments^[18] indicate that the molecular dipole moment must be reduced by more than an order of magnitude. A direct indication of the dipole moment of adsorbed molecules can be obtained from the substrate's work function. From the high-energy cutoff of the photoelectron spectra (Figure 2) it is evident that upon reversing the direction of the layer from C- to N-bound (Figures 2a, c vs b), the work function increases by only about 0.3 eV, whereas for molecules with a dipole moment of about 10 D or more the work function would have dropped by many volts. This means that the dipole moment of the molecules was reduced by two orders of magnitude due to adsorption.^[19] Theory indeed predicts that the molecular dielectric constant will be modified substantially by adsorption as a monolayer.^[14, 20, 21] This means that the electronic structure of the molecules is substantially modified upon adsorption, probably by charge transfer between the metal substrate and the molecule. Apparently, the charge redistribution process results in unpaired electrons on the adsorbed molecules, that is, the adsorbed molecules become paramagnetic.

Still, the questions posed above are not answered. A full description of these phenomena does not yet exist, but the following simple model is compatible with all the observations and correctly predicts the direction of magnetization. Moreover, since the reported phenomena exhibit parallels to some biological membranes, the model may serve as a basis for understanding the effects of magnetic fields on biological systems.

Upon adsorption, a transient current flows through the helix and discharges the electric dipole while inducing

magnetism, like a classical electromagnetic coil. The spins of simultaneously created unpaired electrons adjust accordingly and remain polarized with the support of exchange forces with the metal and the already polarized electrons of attached neighboring helices. The result of such an adsorption mechanism is a magnetic layer in which the direction of the magnetic field is given by Ampere's law. For each adsorbed helix, the original electric dipole polarity and the handedness of the helix determine the direction of the magnetic field along the helical axis.

As can be seen in Figure 1, the helix axes are not well aligned normal to the surface. Therefore, when an external magnetic field is applied in the normal direction, it forces these axes to become closer to or further away from normal, depending on the direction of the external magnetic field. The observed magnetic effects in Figure 1 are consistent with this simple model.

The magnetic properties of the film are the reason for the large spin selectivity in electron transmission. This effect is consistent with the effect in inorganic thin magnetic layers, known as giant magneto spin selectivity^[22, 23] and the related colossal magnetoresistance effect.^[24, 25] Hence, the magnetic properties of the organic films explain their high selectivity for transmission of spin-polarized electrons, an effect that results from the cooperative nature of the film on the metal substrate. The seemingly surprising change in the direction of magnetization on changing the molecular terminus on the gold surface is resolved by the direction of discharge of the electric dipole through the helices.

In conclusion, we found that the adsorption of chiral species in layers converts electric dipoles into magnetic dipoles. Some biological membranes that show similar magnetic orientation effects can be expected to have similar magnetic properties.

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A Nanoporous Metal–Organic Framework Based on Bulky Phosphane Ligands**

Xingling Xu, Mark Nieuwenhuyzen, and Stuart L. James*

Metal–organic frameworks are polymer networks consisting of metal ions connected by organic bridging ligands, and they represent a new approach to the synthesis of nanoporous materials.^[1–11] Applications are therefore anticipated as novel molecular sieves, sensors, ion-exchangers, and catalysts.^[1–10] However, mutual interpenetration of the polymer networks, whereby the vertices of one occupy the cavities of another,^[8, 12] often frustrates attempts to generate large accessible pores. Whereas all previous work in this field has featured N- or O- donor bridging ligands, we report novel results with a bulky triphosphane 1,3,5-tris(diphenylphosphanyl)benzene (**L**; see Figure 1a).^[13, 14] The use of the ligand **L** unex-

pectedly gave a non-interpenetrating network polymer $[\text{Ag}_4\text{L}_3(\text{O}_3\text{SCF}_3)_4]$ (**1**) with remarkably wide (1.60–1.84 nm) channels. In the as-synthesized state these channels appear to be saturated with solvent, which can be exchanged for other solvents, which can be removed by heating under vacuum without collapse of the metal–phosphane framework. The network bulk, imparted by the phenyl groups of **L**, seems to disallow network interpenetration. Because a P-donor ligand was used, ³¹P NMR spectroscopy gives insight into solution-state precursors, which appear to be discrete coordination cages.

We have investigated the coordination-cage and polymer chemistry of multidentate phosphane silver complexes.^[15a–d] For example, the flexible triphosphane $\text{CH}_3\text{C}(\text{CH}_2\text{PPh}_2)_3$ (triphos) unexpectedly gave the hexasilver adamantanoid cage $[\text{Ag}_6(\text{triphos})_4(\text{triflate})_4]^{2+}$ (triflate = trifluoromethanesulfonyl).^[15a] Given the differences in behavior of flexible^[16] and rigid^[15b,c] diphosphanes, we were interested in how the rigid triphosphane **L** would behave. Polymer **1** was obtained by diffusing diethyl ether into a chloroform–nitromethane solution containing a 3:2 molar ratio of silver trifluoromethanesulfonate (silver triflate, AgOTf) and **L**. Polymer **1** was initially isolated as hexagonal crystals in 10% yield, the remainder of the product being a powder which X-ray diffraction showed to be amorphous.^[17] A single-crystal X-ray analysis of **1**,^[18] performed on a crystal which was mounted rapidly after removal from the supernatant, and cooled to 120 K, revealed a two-dimensional network of hexagonal rings (Figure 1b). The large 72-atom rings contain 18 silver atoms and 12 **L** units. The network nodes are trigonal-planar silver centers bonded to three **L** units, with neighboring triflate anions which are too distant for significant bonding interactions ($\text{Ag} \cdots \text{O}$ distance 3.25(1) Å). The connectors between the nodes are Ag_2L_2 groups which have a 12-membered ring structure. The pairs of silver centers in these smaller rings each bond to two P atoms and are bridged by two weakly coordinated triflate anions, each making two $\text{Ag} \cdots \text{O}$ contacts of 2.73(1) and 2.93(1) Å. The CF_3 groups of these triflate anions point towards the centers of the large rings, to give a transannular $\text{F} \cdots \text{F}$ distance of 19.01(3) Å, which corresponds to approximately 16.0 Å when the van der Waals radius of fluorine (1.47 Å^[19]) is taken into account. The transannular $\text{H} \cdots \text{H}$ distance between phenyl groups is 20.8 Å, which gives a major ring diameter of around 18.4 Å when the H van der Waals radius of 1.20 Å^[19] is taken into account. The honeycomb layers stack in an eclipsed fashion, so that a three-dimensional structure of approximately cylindrical channels is generated. A space-filling representation of a segment of the framework (nine channels and five layers), which includes the phenyl groups, is shown in Figure 1c. These channels are amongst the widest reported so far for a coordination network. In fact, the calculated “free sphere” (i.e. the largest sphere which could move freely throughout the structure, a parameter introduced by Yaghi and co-workers^[20]) of diameter 16.0 Å may be the largest of any characterized crystal. Of note is the superficial similarity of **1** to the liquid crystal templated SiO_2 -framework MCM-41s,^[21, 22] which have channel diameters of around 15 to 100 Å, but are not ordered at the atomic level. Based on a spherical

[*] Dr. S. L. James, Dr. X. Xu, Dr. M. Nieuwenhuyzen
School of Chemistry
The Queen's University of Belfast
David Keir Building, Stranmillis Road, Belfast, Northern Ireland BT9 5AG (UK)
Fax: (+44)2890382117
E-mail: s.james@qub.ac.uk

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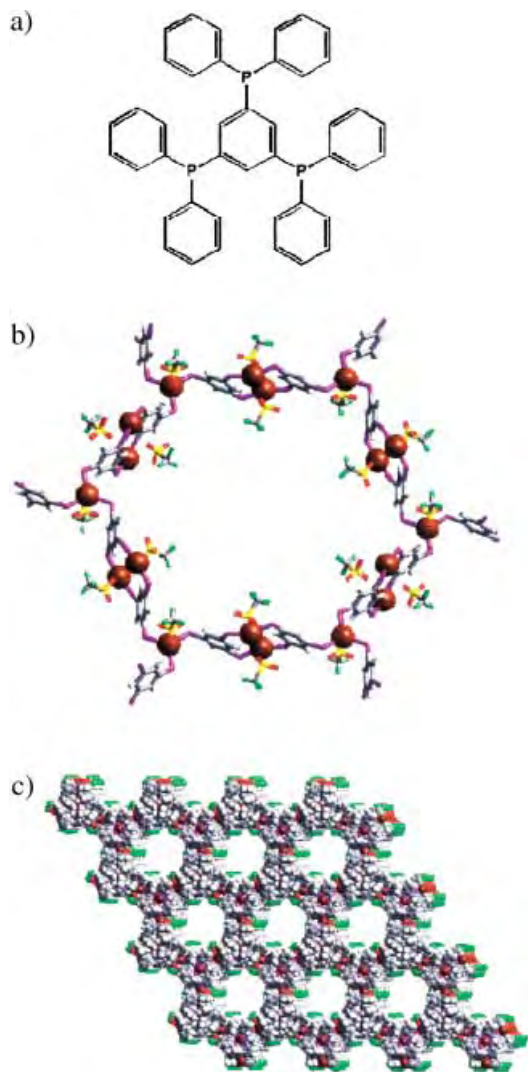


Figure 1. a) Structure of ligand **L**; b) hexagonal network structure of polymer **1** (the bulky phenyl substituents are omitted for clarity); c) space-filling view of a crystal segment of **1** showing the channel structure (C = gray, H = white, P = pink, F = green, Ag = brown, S = yellow, O = red).

1.20 Å probe, the accessible volume is 35.7 % ($0.37 \text{ cm}^3 \text{ g}^{-1}$) of the total, and the accessible channel surface area is 2015 Å^2 per unit cell ($1032 \text{ m}^2 \text{ g}^{-1}$). The X-ray analysis revealed only electron-density peaks corresponding to less than one electron Å^{-3} in the channel space. These peaks presumably result from disordered solvent molecules (see below), the presence of which is supported by the relatively high R factor of 0.0906. Yields of polymer **1** increased to 50–80 % by using the appropriate 4:3 AgO_3SCF_3 :**L** stoichiometry in 3:7 nitromethane:ethanol as solvent. This solution was partially evaporated at 88°C to give a mixture of block and hexagonal crystals together with some amorphous material.^[17] After removing these crystals from their supernatant solution, they were washed with ethanol and kept under ambient conditions for 48 h. A single-crystal X-ray analysis on a block^[23] yielded essentially the same structure as **1** in which the largest electron-density peak within the channels was 0.86 electrons Å^{-3} , although with a slightly lower R factor of 0.0632. The structural homogeneity of the crystalline product was sup-

ported by powder X-ray diffraction, which gave a pattern matching that calculated from the single-crystal structure determination. The crystals appeared indefinitely stable when immersed in alcohols, diethyl ether, water, aromatic, and chlorinated solvents, but were dissolved by acetonitrile.

Although the elemental analysis of the as-synthesized compound could be fitted to the formula $[\text{Ag}_4\text{L}_3(\text{O}_3\text{SCF}_3)_4] \cdot (\text{CH}_3\text{NO}_2)_{1-2}$, it should be noted that since the carbon content of ethanol is very close to that of the framework, this formula likely to be misleading (see below). Thermogravimetric analysis (TGA) showed 2 % weight loss on heating to 80°C (at a heating rate of $10^\circ\text{C min}^{-1}$), which corresponds to the loss of one nitromethane molecule per $[\text{Ag}_4\text{L}_3(\text{O}_3\text{SCF}_3)_4]$ formula unit, before rapid weight loss began at 400°C . The disparity between this result and those from the prolonged heating experiments (see below) may indicate that thermally induced loss of solvent was too slow to register fully in the TGA experiment.

The thermal stability of as-synthesized **1** was tested by heating samples to a given temperature, at a rate of $10^\circ\text{C min}^{-1}$, maintaining them at this temperature for 1 h, and then analyzing them by powder X-ray diffraction. This approach revealed that between 170 and 200°C a change did indeed take place to a give material which showed some evidence of a second crystalline phase, which we will report more fully in due course.

To establish whether the structure was stable in the absence of guests, a number of samples were subjected to reduced pressure and/or heated. X-ray powder diffraction patterns were then obtained to examine the integrity of the structure. Part of each sample was also dissolved in $[\text{D}_3]$ acetonitrile, and ^1H NMR spectra were recorded and used to check for residual solvents by comparing the integrated intensity of solvent peaks with that of the aromatic signals of the ligand. After 12 h at 0.1 mmHg, the powder diffraction pattern was unchanged, but ^1H NMR spectroscopy revealed that the sample still contained large amounts of ethanol (ca. 14 molecules per $\text{Ag}_4\text{L}_3(\text{OTf})_4$ formula unit, which corresponds to ca. 75 % occupation of the available channel volume). When a sample was immersed in diethyl ether for 12 h, then heated to 130°C at 0.1 mmHg for 12 h, the diffraction pattern was again unchanged, but approximately three molecules of diethyl ether and three molecules of water were still present per $\text{Ag}_4\text{L}_3(\text{OTf})_4$ formula unit, which corresponds to a total of around 60 % of the available channel volume. Interestingly, no ethanol was detected, which shows that included guests can be exchanged by immersing the crystals in a second liquid. A third sample was immersed in dichloromethane for 12 h, then heated to 170°C , at 0.1 mmHg, for 24 h. The powder diffraction pattern was again unchanged, and no dichloromethane was detected by NMR spectroscopy, although there were apparently about two molecules of water present per $\text{Ag}_4\text{L}_3(\text{OTf})_4$ formula unit, this corresponds to around 4 % of the available channel space. Therefore, it seems possible to obtain virtually solvent- and water-free **1**, without collapse of the framework.

The large-diameter rings in **1** are very striking, given the frequent occurrence of network interpenetrating in coordination polymers.^[12] Interpenetration may be prevented in this

case by the unusually high steric bulk of the network. A solid cylindrical ring with internal diameter d , edge width w , and depth p can be considered as a simple model for the ring structure of polymer **1** (Figure 2a). Interpenetrating orthogonal rings are shown in Figure 2b, and again in Figure 2c, with

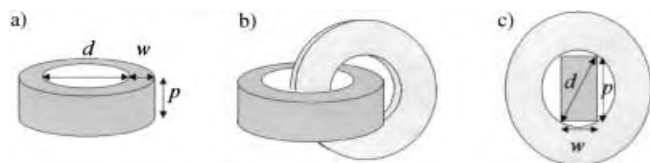


Figure 2. a) Labeling system for dimensions of a solid circular ring, d = inner diameter, w = edge width, p = depth; b) two such rings interpenetrating; c) limiting situation for the two interpenetrating rings, revealing the geometric constraint $d^2 \geq w^2 + p^2$.^[24]

one ring in cross-section. This model reveals that the relationship $d^2 \geq w^2 + p^2$ must be satisfied for interpenetration to occur.^[24] There is some ambiguity in defining d , w , and p for compound **1**, because it is not perfectly regular, nor perfectly rigid, and so some intermeshing of the surfaces of interpenetrating networks would occur. However, accepting this caveat, w was taken as 13.9 Å (non-transannular F(1)⋯F(1) distance of 10.99 Å plus 2.94 Å for van der Waals radii^[19]) and a lower estimate of p taken as 12.9 Å (which is half of the unit cell dimension c , and allows for intermeshing of the layer surfaces). This model requires a minimum “interpenetrating” d value of 18.9 Å at the in-pointing triflates. The actual value of 16.0 Å is only 85% of this, which suggests that the dimensions of **1** are probably transgressing their permitted values for interpenetration. A geometric model for interpenetrated cubic metal–organic frameworks with bulky spherical vertices has been described by Yaghi and co-workers.^[8] The structure of **1** points to an alternative general situation, in which the network as a whole is too bulky to permit interpenetration.

³¹P NMR spectroscopy was used to probe the nature of solution-state precursors to network **1**. In 4:1 deuterochloroform:nitromethane as solvent, with a 3:2 molar ratio of silver triflate and **L**, where the concentration of **L** was 25 mmol L^{−1} as in the original synthesis, two species were observed, denoted **A** and **B** (Figure 3a). Both had highly symmetrical structures, as indicated by their single phosphorus chemical environments, and displayed well-resolved one-bond couplings to the spin-1/2 silver isotopes ¹⁰⁷Ag and ¹⁰⁹Ag. Chemical shift (δ) and coupling ($^1J_{109\text{Ag},31\text{P}}$ Hz) data, respectively, for **A** are 15.0, 594, and, for **B**, 13.7 and 557. The magnitudes of the coupling constants indicate that each silver center is coordinated to two P atoms.^[25] Spectra were concentration-dependent, with dilution increasing the amount of **A** relative to **B**, and causing the appearance of a third species **C**. This species exhibited similar spectroscopic parameters, with $\delta = 16.0$, and $^1J_{109\text{Ag},31\text{P}} = 560$ Hz. These observations point to equilibria between symmetrical cage compounds of general formula $[\text{Ag}_3\text{L}_2(\text{O}_3\text{SCF}_3)_3]_n$. Two examples of possible structures, which correspond to $n = 1$ and 2, are depicted in Figure 3b. Supporting evidence for the precursor cages was provided by electrospray mass spectrometry. A solution similar to that used for NMR spectroscopy, but at a ligand concentration of

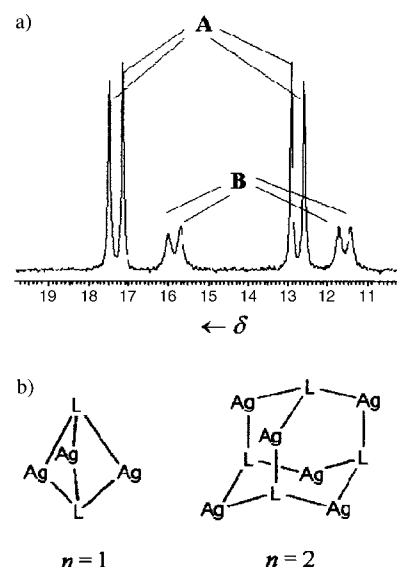


Figure 3. a) ³¹P NMR spectrum in 4:1 chloroform:nitromethane of a 3:2 AgO_3SCF_3 :**L** mixture, at a ligand concentration of 25 mmol L^{−1}; b) Examples of possible $[\text{Ag}_3\text{L}_2]_n$ cage structures formed by Ag_3L_2 mixtures corresponding to the high molecular symmetry implied by ³¹P NMR signals.

about 12.5 mmol L^{−1}, with methanol as the mobile phase, gave rise to mass peaks corresponding to the $n = 1$ (trinuclear) cage in which two, one, and zero triflate anions were coordinated (m/z 528, 866, and 1882, respectively). In addition, a peak at 1205 was observed which corresponds to the tricationic $n = 2$ cage with three coordinated triflate anions. A signal also occurred at m/z 1311, which corresponds to the dication $[\text{Ag}_4\text{L}_5(\text{OTf})_2]^{2+}$, which has the same ligand-to-metal stoichiometry as the polymeric framework. Although such a species seems, therefore, to be the most logical precursor to polymer **1**, it is, at most, a minor species in solution since it could not have equivalent phosphorus centers, and so does not correspond to any of the species visible in the NMR spectra. The absence of peaks for higher nuclearity cages may be because of the low sample concentration necessary for the mass spectrometry experiment (lower than for the NMR spectra), and/or the upper m/z detection limit of the mass spectrometer (3000). Although definite identities cannot be assigned to the NMR-visible species **A**, **B**, and **C**, it can be concluded that ring-opening of one or more coordination cage precursors^[15c,e,f] constitutes part of the pathway to polymeric **1**.

In summary, **1** is an unusual nanoporous metal–organic framework, which suggests further potential for bulky and NMR-friendly building blocks for synthesizing, and understanding the formation of, stable nanoporous materials.

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- [17] Initial synthesis of **1**: A solution of 1,3,5-tris(diphenylphosphanyl)-benzene (**L**; 63 mg, 0.1 mmol) in CH₂Cl₂ (3 mL) was added to a solution of AgOTf (38.5 mg, 0.15 mmol) in CH₃NO₂ (1 mL). Diffusion of diethyl ether vapor into the resulting solution over one week gave colorless hexagonal crystals of **1** in 10% yield, together with powdery amorphous material. Higher yield synthesis: 1,3,5-tris(diphenylphosphanyl)-benzene (**L**; 31.5 mg, 0.05 mmol) and AgOTf (17.0 mg, 0.067 mmol) were dissolved in a mixture of ethanol (7 mL) and nitromethane (3 mL), placed in a loosely stoppered polypropylene flask and partially evaporated at 88 °C overnight. Block and hexagonal colorless crystals were manually separated from the powdery amorphous byproduct. Yield: 50–80%; elemental analysis calcd (%) for [Ag₃(OTf)₄]·CH₃NO₂: C 52.79, H 3.42; found: C 52.55, H 3.32.
- [18] X-ray data were collected on a Bruker AXS SMART diffractometer using the SAINT-NT^[26] software with omega/phi scans. A crystal was mounted on to the diffractometer under dinitrogen at approximately 120 K. The structure was solved using direct methods with the SHELXTL program package.^[27] Crystal Data for the hexagonal plate crystals [C₁₃₀H₉₉F₁₂Ag₄P₉S₄O₁₂]_n (**1**): *M* = 2919.54, hexagonal, space group *P*3̄c, *a* = 29.949(8), *c* = 25.929(10) Å, *V* = 20 141(11) Å³, *Z* = 4, *μ* = 0.545 mm^{−1}. A total of 39 337 reflections were measured for the angle range 4 < 2θ < 45 and 8797 independent reflections were used in the refinement. The final parameters were *w*R₂ = 0.3009 and *R*₁ = 0.0906 [*I* > 2σ(*I*)]. Cell parameters for the block crystals [C₁₃₀H₉₉F₁₂Ag₄P₉S₄O₁₂]_n (**1'**)^[23]: *M* = 2919.54, hexagonal, space group *P*3̄c, *a* = 30.076(1), *c* = 25.791(1) Å, *V* = 20 204(1) Å³. The residual densities (< 1 electron Å^{−3}) associated with the voids indicate small amounts of very diffuse solvent molecules. Consequently, the nature of the solvent could not be determined using X-ray diffraction methods. Powder diffraction measurements were performed on a Siemens D5000 powder diffractometer in continuous mode with step size of 0.02° and step time of 20 s. ³¹P NMR spectra were obtained at 121 MHz and 25 °C and are referenced to external 85% phosphoric acid (δ = 0). CCDC 170632 (**1**) and 176871 (**1'**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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- [23] A cell check was undertaken on a crystal from a batch that had been washed with ethanol and dried in air for 2 days which gave cell parameters *a* = *b* = 30.076(2), *c* = 12.8958(8) Å *γ* = 120° indicating the presence of a possible polymorph with a *c* axis half that of the original cell. The data was collected and processed using these cell parameters, however, subsequent attempts at structure determination in this cell were unsuccessful. Thus we concluded the apparent halving of the *c* axis in this crystal was incorrect and after transformation to the larger cell *a* = *b* = 30, *c* = 25 Å, *γ* = 120° the structure was shown to be the same as previously determined with a *w*R₂ = 0.22 and *R*₁ = 0.0632.
- [24] This ignores the effect of curvature within the cavities, which would place slightly more stringent limits on *p* and *w* for a given cavity size.
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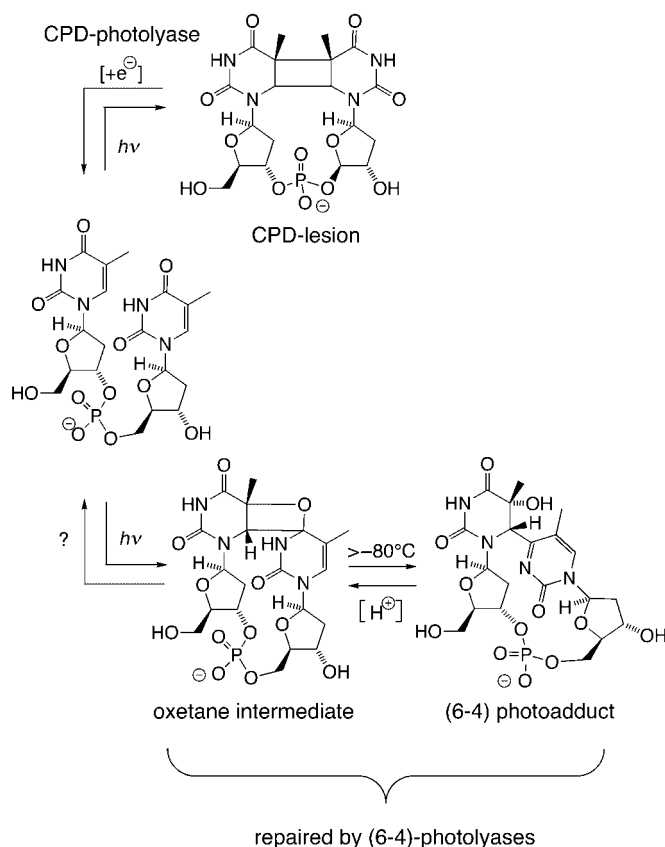
A (6-4) Photolyase Model: Repair of DNA (6-4) Lesions Requires a Reduced and Deprotonated Flavin**

Michaela K. Cichon, Simone Arnold, and Thomas Carell*

Ultraviolet irradiation of cells causes the formation of a variety of DNA lesions with known mutagenic, carcinogenic, and lethal effects.^[1, 2] The main UV lesions are cyclobutane–pyrimidine dimers (CPD lesions) formed in a photochemically allowed [2π + 2π] cycloaddition and (6-4) photoadducts; the latter are presumably more mutagenic.^[3, 4] The highly mutagenic (6-4) lesions are believed to be formed in a Paternó-Büchi reaction between two adjacent pyrimidines in the DNA duplex to give initially an oxetane intermediate, which rearranges above −80 °C to the (6-4) photoadduct by a proton shift and a C–O bond scission (Scheme 1).^[5] Both types of DNA lesions are repaired in many organisms by a special class of repair enzymes, namely DNA photolyases, which cleave both lesions back into the monomers in a light-dependent, single electron transfer based repair reaction.^[6] In the last decade, crystallographic,^[7, 8] enzymatic,^[9, 10] and model compound studies^[11–14] showed that the photolyases,^[15] which are responsible for the repair of CPD lesions, contain a

[*] T. Carell, M. K. Cichon, S. Arnold
Fachbereich Chemie, Philipps-Universität Marburg
Hans-Meerwein-Strasse, 35032 Marburg (Germany)
Fax: (+49) 6421-2822189
E-mail: carell@mail.uni-marburg.de

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Scheme 1. Depiction of the formation and repair of the mutagenic cyclobutane pyrimidine dimer lesion (CPD lesion) and of the (6-4) photoadduct via the key oxetane intermediate.

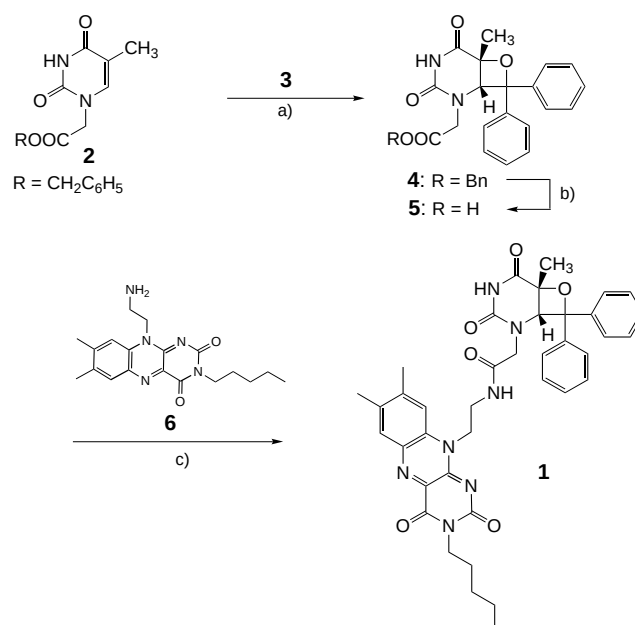
reduced and deprotonated flavin (FADH^-),^[13, 16] which upon excitation by light, donates one electron to the CPD dimer. This cleaves (cycloreverts) spontaneously into its radical anion. In contrast, the (6-4) photolyases,^[17, 18] which exclusively repair (6-4) lesions,^[19] are less well characterized, and the repair mechanism is currently not understood.^[20, 21]

Based on the sequence homology between CPD and (6-4) photolyases and because both repair enzymes contain an FAD coenzyme, Kim et al. proposed a repair mechanism.^[18] Their model postulates that binding of the (6-4) lesion induces a back rearrangement of the (6-4) photoadduct into the oxetane.^[22] Calculations predict that this rearrangement could be energetically too costly to proceed spontaneously within the active site of the enzyme.^[23] Recently, however, two histidine residues that catalyze the putative oxetane formation were identified.^[22] The key premise of the mechanism proposed by Kim et al. is the rapid cleavage of the oxetane intermediate by a light-induced electron transfer. Quantum chemical calculations (in the gas phase) predict that oxetanes cleave spontaneously after single electron donation or after single electron abstraction.^[24] Laser flash photolysis experiments by Falvey and co-workers^[25] and Miranda et al.^[26] recently provided experimental evidence that oxetanes do indeed split in the presence of various electron donors and acceptors in a light-dependent reaction.^[27] So far, experiments which could clarify the function of the flavin coenzyme in (6-

4) photolyases and in particular the direction of the electron transfer within the enzyme active site are not reported. A preliminary study by Falvey and coworkers, however, provided evidence that a light-induced oxetane cleavage could be possible with a reduced and also with an oxidized flavin, although these studies were hampered by decomposition of the flavin.^[28] For a deeper understanding of one of nature's most important genome-repair processes, the direction of the electron transfer needs to be clarified.

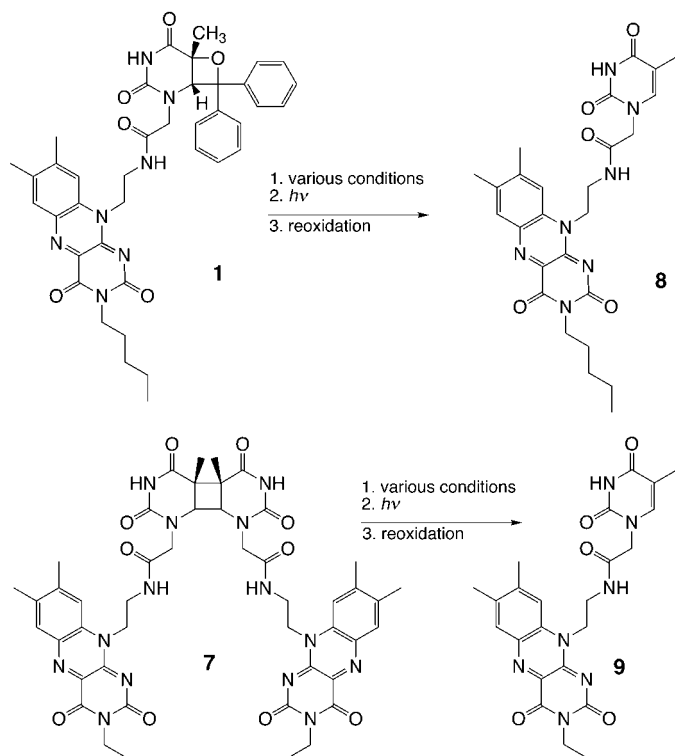
Herein we report for the first time about flavin-induced oxetane-splitting experiments that use the covalently linked flavin- and oxetane-containing model compound **1** (Scheme 2). We found that **1** is able to mimic the critical putative cycloreversion step catalyzed by DNA (6-4) photolyases with a high quantum yield. We show that the flavin-induced splitting of the oxetane is only possible through the reductive pathway. The cycloreversion is induced by single electron donation to the oxetane and strictly requires the flavin in its reduced and deprotonated state. The results prove a close mechanistic relationship between CPD and (6-4) photolyases.^[29]

The synthesis of the (6-4) photolyase model compound **1** required for this study and the chemistry of the cleavage reaction is depicted in Schemes 2 and 3. Irradiation of **2** in the presence of benzophenone (**3**) furnished the stable oxetane **4**, which was isolated by flash chromatography. This oxetane is supposed to model the unstable putative oxetane intermediate. Hydrogenolytic cleavage of the benzyl ester and condensation of the obtained oxetane acid **5** with 10-aminoethylflavin **6** furnished model compound **1** after flash chromatography as a yellow powder ready for mechanistic studies.



Scheme 2. Synthesis of (6-4) model compound **1**. a) benzophenone (**3**), $h\nu$, acetonitrile, 6 h, 18%; b) Pd/C, acetic acid, room temperature, 3 h, 57%; c) HOBT, TBTU, DMF, room temperature, 2 h, 92%. HOBT = 1-hydroxy-1*H*-benzotriazole; TBTU = 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate; DMF = *N,N*-dimethylformamide.

To uncover directly potential mechanistic similarities or differences between (6-4) and CPD photolyases, we performed most of our studies with a 1:1 mixture of the (6-4) model compound **1** and the well-studied CPD photolyase model compound **7**^[30] under direct competition conditions (Scheme 3). To allow rapid separation by HPLC of the model compounds **1** and **7** and of the cleavage products **8** and **9**, the flavins in **7** and **9** contain an ethyl side chain at N3, and the flavins in **1** and **8** possess a pentyl side chain at N3.



Scheme 3. Cleavage reaction of **1** and **7** to form **8** and **9**, respectively.

To investigate whether oxetane splitting is possible by an oxidized flavin, a solution of both model compounds **1** and **7** in ethylene glycol (10^{-5} M– 10^{-6} M) was prepared and irradiated with monochromatic light (366 nm) in a fluorimeter. We performed these experiments twice: once under anaerobic and once under aerobic reaction conditions. The results were, however, the same. During the irradiation experiments, samples were taken from the assay solution after defined time intervals with the help of a microsyringe and analyzed by reversed-phase HPLC. The results of all the experiments are summarized in Figure 1. Chromatogram 1 (Figure 1) shows the elution profile of the model compound mixture (**1** + **7**) after 0 min of irradiation. The oxetane model compounds **1** and the CPD model compound **7** elute with very different retention times at 22.7 min and at 9.1 min, respectively. Chromatogram 2 (Figure 1) was obtained after irradiation of the mixture for more than 1 h. None of the two expected reaction products **8** and **9** were detected, showing that the oxidized flavin is unable to initiate the splitting of the oxetane and of the CPD lesion. Since the reduction potential of the

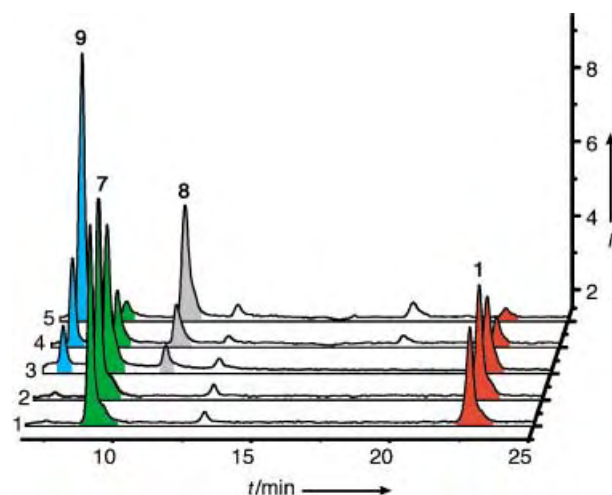


Figure 1. Chromatograms (HPLC) obtained during the various irradiation experiments. Elution times **9**: 7.4 min, **7**: 9.1 min, **8**: 11.3 min, **1**: 22.7 min. Conditions: Nucleosil C18-column (5×250 mm), detection at 450 nm, gradient: A = water, B = acetonitrile, 60% A to 30% A in 25 min, flow rate: 0.7 mL min^{-1} .

light-excited flavin is about $E_{\text{red}}^* = 1.7 \text{ V}$, the results show that the oxidation potential of the oxetane could be $E_{\text{ox}} > 1.7 \text{ V}$.

To investigate the possibility of splitting the oxetane reductively, we stoppered another assay solution that contained a mixture of **1** and **7** with a rubber septum, and purged the solution intensively with nitrogen for 20 min to establish anaerobic conditions. Upon addition of a reducing sodium dithionite solution, the flavin fluorescence vanished. The UV spectrum of the sample proved the presence of the reduced flavin under these conditions. The solution was again irradiated at 366 nm. The HPLC chromatogram of a sample taken after 1 h of irradiation and subsequent rigorous reoxidation of the flavin through shaking exposed to air for about 12 h is depicted in Figure 1 (trace 3). To our surprise, only a small amount of the expected cleavage products **8** and **9**, which separate well (11.3 min and 7.4 min), were formed, which shows that the reduced flavin coenzyme is also almost inactive as a photosensitizer. Independent irradiation studies of both model compounds confirm that the oxetane and the CPD dimer do not cleave efficiently under these “just-reductive” conditions. For the CPD photolyases, it was shown that efficient dimer splitting strictly requires deprotonation of the reduced flavin.^[13, 16] To investigate how flavin deprotonation affects the critical oxetane cycloreversion, we added triethylamine to the assay solution to ensure deprotonation of the N1-H ($\text{p}K_{\text{a}} \sim 6.5$)^[31] of the reduced flavin. Within a few minutes of irradiation of the assay solution under these basic reaction conditions, both model compounds **1** and **7** had been converted significantly into the cleaved products **8** and **9**. Trace 4 (Figure 1) depicts the result obtained after irradiation for 20 min. Trace 5 (Figure 1) represents the reaction mixture after 60 min of irradiation. An independent study of the oxetane model compound **1** shows that under these conditions, oxetane cleavage proceeds with a half-life of about 20 min. When the same solution was kept in the dark, no oxetane cleavage occurred, which proves that the cycloreversion is, indeed, a light-induced process. Addition of

acetic acid to the assay solution stops the cycloreversion reaction immediately, thus underlining the strict requirement for basic conditions. Irradiation of oxetane **4** in the presence of flavin **6** under otherwise identical conditions does not result in any oxetane cleavage, which clearly shows that the splitting reaction is an intramolecular reaction.

To determine the efficiency of the oxetane and CPD model compounds, we determined the quantum yields for the model repair reaction (Figure 2). Cleavage of the oxetane proceeds with a quantum yield of 0.3% under neutral conditions (Figure 2, bar 4) and not at all in the presence of acid (Figure 2, bar 5). Under basic conditions, however, oxetane splitting is twice as efficient ($\phi = 2.3\%$, Figure 2, bars 1 and 3) as CPD cleavage ($\phi = 1\%$, Figure 2, bar 2). This high quantum efficiency is in full agreement with a recent laser flash photolysis experiment by Falvey and co-workers which shows that oxetane ring opening is faster than CPD cleavage.^[25] The quantum yield of 2.5% for a model compound compares well with the photolyase repair quantum yield of approximately 50%, which shows that our new model compound **1** mimics the repair reaction remarkably well.

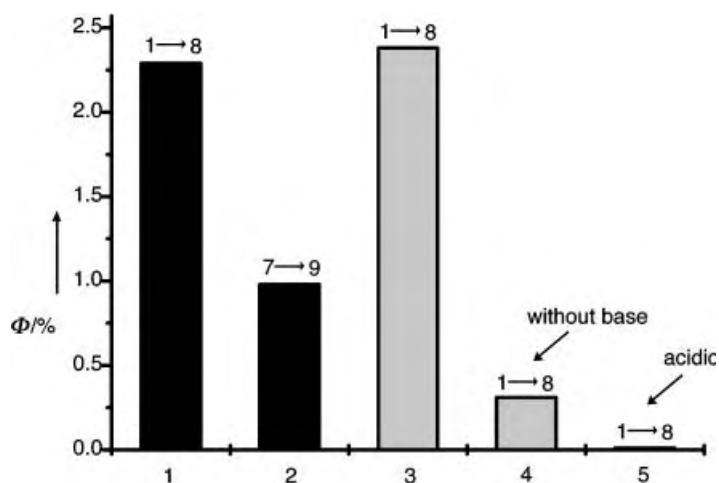


Figure 2. Bar graph of the measured quantum yields. Black bars (one experiment): results from the direct competition experiment **1** + **7** to give **8** + **9**. Grey bars: results from independent studies as indicated above the graphs. Conditions: ethylene glycol solutions. Bar 1: oxetane model **1** ($c = 4 \times 10^{-6}$ M); Bar 2: CPD model **7** ($c = 2 \times 10^{-6}$ M); Bars 3–5: **1** + **7** ($c = 1.0 \times 10^{-4}$ M).

In summary, we prepared and investigated the first covalently linked model compound for the DNA (6-4) photolyase. We showed that the oxidized flavin and the reduced, but not deprotonated, flavin are unable to repair efficiently. Oxetane splitting clearly requires the reduced and deprotonated flavin. The result suggests that, in agreement with the mechanism proposed by Kim and co-workers, electron transfer proceeds from the flavin to the oxetane as the key step of the repair reaction. The strict requirement to deprotonate the flavin suggests that an electron transfer from the neutral FlH_2 to the oxetane is either not possible or provides a zwitterionic intermediate $\text{FlH}_2^{+} - \text{oxetane}^{-}$, which is too short-lived to allow oxetane cleavage to compete

with back electron transfer. Instead, deprotonation furnishes a more potent flavin donor FlH^{-} , which gives a charge-shift intermediate $\text{FlH}^{+} - \text{oxetane}^{-}$ after electron transfer. The lifetimes of this intermediate now needs to be measured to gain further insight into one of nature's most important genome repair processes. The important fact that the cleavage of the CPD dimer in model compound **7** and oxetane splitting in model compound **1** proceed fastest under identical conditions (reduced and deprotonated flavin coenzyme) provides strong support for a very similar mechanism.

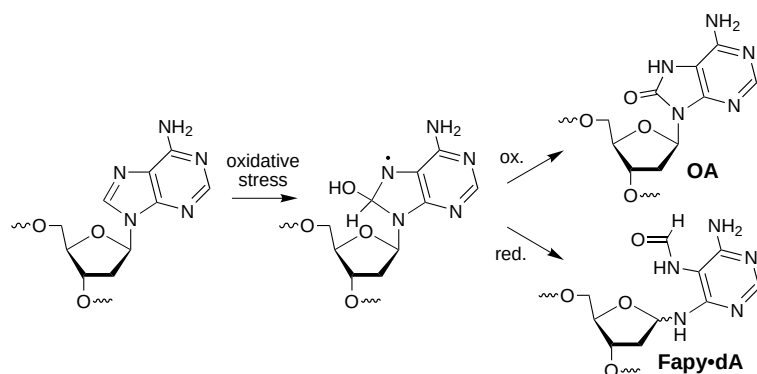
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Fapy·dA Induces Nucleotide Misincorporation Translesionally by a DNA Polymerase**

Michael O. Delaney, Carissa J. Wiederholt, and Marc M. Greenberg*

DNA is constantly exposed to endogenous and exogenous agents that modify its structure. DNA damage can give rise to mutations, which in turn can result in diseases such as cancer. Understanding the effects of individual lesions on the structure and function of DNA helps provide an understanding at the molecular level of the origin of genetically based diseases.^[1] When deoxyadenosine in DNA is exposed to oxidative stress, the respective formamidopyrimidine (Fapy·dA) and 8-oxopurine (OA) lesions are produced from a common intermediate (Scheme 1).^[2] Under O₂-deficient conditions, radiolysis of mammalian chromatin produces



Scheme 1. Formamidopyrimidine (Fapy·dA) and 8-oxopurine (OA) lesions produced from a common intermediate, upon exposure of deoxyadenosine in DNA to oxidative stress.

Fapy·dA in greater amounts than OA. The respective lesions derived from deoxyguanosine are formed in comparable relative yields.^[2] A recent study on human tumor cells indicates that the purine lesions derived from deoxyguanosine are formed tenfold more readily than Fapy·dA and OA.^[3] Very little is known about the mutagenicity of Fapy·dA, because biopolymers that contain Fapy·dA at defined sites were unavailable. Recently, we developed a method for the chemical synthesis of oligonucleotides that contain Fapy·dA and configurationally stable analogues at defined sites, and wish to provide the first report of the effect of these molecules on the fidelity of a DNA polymerase.^[4]

Previous studies on the effects of Fapy·dA on polymerase activity relied on inferential evidence in which yields of randomly formed lesions were correlated with mutations that involved deoxyadenosine (dA).^[5] Based on these studies, it was proposed that Fapy·dA induces misincorporation of

dCTP opposite itself by adopting a *syn* conformation and thus presenting a deoxyguanosine (dG)-like hydrogen-bonding pattern. The N7-methylated analogue (MeFapy·dA) produced by methylation followed by hydrolytic ring opening cannot present a comparable dG-like hydrogen-bonding pattern, but was also proposed to direct the incorporation of dCTP. In contrast, in vitro and in vivo experiments on OA are unequivocal, thanks to the development of methods for synthesizing oligonucleotides that contain the lesion at defined sites.^[6, 7] These studies revealed that dG was the most likely nucleotide to be incorporated opposite the lesion, other than thymidine (T).^[7, 8] Structural studies suggested that the lesion forms a series of bifurcated hydrogen bonds to dG when it is present in the *syn* conformation.^[9]

The kinetics for the insertion of the individual native nucleotides by Klenow *exo*⁻ were measured opposite an equilibrium mixture of α - and β -Fapy·dA in a 30-mer template under single-hit conditions by using a standing start (Table 1).^[10] For comparison, measurements were also made by using an otherwise identical template that contained dA instead of Fapy·dA. Incorporation ($V_{\max}/K_m$) of thymidine (T) and deoxycytidine (dC) opposite Fapy·dA decreased almost fourfold and sixfold, respectively, relative to that observed when a template that contained dA was used. The latter observation is contrary to that anticipated based on conclusions reached in previous indirect studies of Fapy·dA.^[5] In contrast, the frequency (F_{ins}) of misincorporation of dA and dG was almost 50 % greater when Fapy·dA replaced the native nucleotide in the template. The significance of these observations is magnified when the F_{ins} of dA and dG opposite Fapy·dA are compared to that of OA, which were reported previously.^[7, 11] Misinsertion frequencies for the control templates that contain dA were remarkably similar in these independent experiments, despite differences in the local sequences of the templates, and utilization of Klenow in studies on OA. In contrast to the observations described with Fapy·dA (Table 1), the F_{ins} of dA, dC, and dG decreased when dA was

Table 1. Kinetic parameters of nucleotide insertion opposite Fapy·dA.
3'-d(T A C C C T G C A C G A C A X T C A C G T G C A A C T T G C)
5'-d(A T G G G A C G T G C T G T G T

		Klenow <i>exo</i> ⁻ dNTP				
		3'-d(T A C C C T G C A C G A C A X T C A C G T G C A A C T T G C) 5'-d(A T G G G A C G T G C T G T G T N				
X	dNTP	K_m [μM]	$V_{\max}$ [% min ⁻¹]	F_{ins} [a]	F_{rel} [b]	
A	T	0.13	4.9	1.0	—	
A	A	147.7	18.7	2.9×10^{-3}	—	
A	G	231.1	9.9	9.9×10^{-4}	—	
A	C	76.3	8.1	2.4×10^{-3}	—	
Fapy·dA	T	0.34	3.8	0.28	1.0	
Fapy·dA	A	86.7	14.7	3.9×10^{-3}	1.4×10^{-2}	
Fapy·dA	G	16.3	1.4	1.5×10^{-3}	5.4×10^{-3}	
Fapy·dA	C	75.2	1.0	4.3×10^{-4}	1.5×10^{-3}	

[a] $F_{\text{ins}} = (V_{\max}/K_m, X = A, \text{dNTP} = T)/(V_{\max}/K_m, X = A \text{ or Fapy·dA}, \text{dNTP} = T, A, G, \text{ or } C)$. [b] $F_{\text{rel}} = (V_{\max}/K_m, X = \text{Fapy·dA}, \text{dNTP} = T)/(V_{\max}/K_m, X = \text{Fapy·dA}, \text{dNTP} = T, A, G, \text{ or } C)$.

[*] Prof. Dr. M. M. Greenberg, M. O. Delaney, C. J. Wiederholt
Department of Chemistry, Colorado State University
Fort Collins, CO 80523 (USA)
Fax: (+1) 970-491-7972
E-mail: mgreenbe@lamar.colostate.edu

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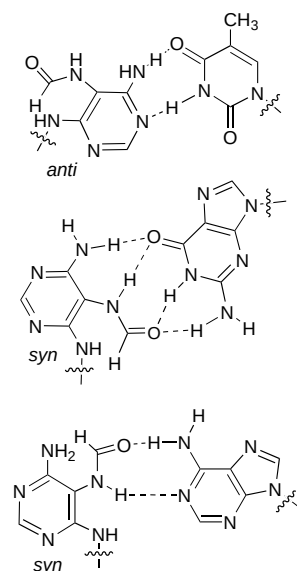
Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

replaced in the template by OA.^[7,11] Comparing the F_{ins} for the independent experiments reveals that Fapy·dA was almost eight times more likely to induce the Klenow enzyme to incorporate dA and three times more likely to incorporate dG opposite itself than was OA. Furthermore, comparison of the K_{m} values (Table 1) indicate that the above preferences result from specific interactions between Fapy·dA and the incoming nucleotide. The implied preferences for Fapy·dA binding to dA and dG are supported by UV-melting studies on dodecamers (Table 2). Duplexes that contain Fapy·dA base paired to dA and dG are stabilized relative to the respective complexes that contain dA in the opposing strand.

Table 2. Comparison of thermodynamic properties of duplex melting between dA and Fapy·dA.

5'-d(T G C A C T X A C A G C) 3'-d(A C G T G A Y T G T C G)			
X:Y	ΔG_{298}° [kcal mol ⁻¹]	X:Y	ΔG_{298}° [kcal mol ⁻¹]
A:T	14.61	Fapy·dA:T	12.97
A:A	10.40	Fapy·dA:A	11.46
A:G	12.60	Fapy·dA:G	13.01
A:C	10.54	Fapy·dA:C	9.82

The preference exhibited by oligonucleotides that contain Fapy·dA to interact with dA and dG in kinetic and thermodynamic experiments can be rationalized by hydrogen-bonding patterns that involve the *syn* conformation of the β -isomer, which differ with respect to the orientation of the formamide group (Scheme 2). The thymidine-like hydrogen-bonding pattern relieves possible steric interactions between

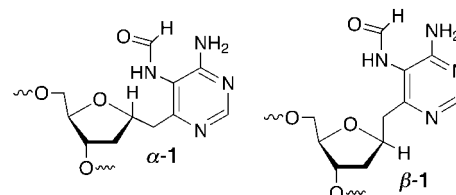


Scheme 2. Oligonucleotides that contain Fapy·dA interact preferentially with dA and dG in kinetic and thermodynamic experiments. This can be rationalized by hydrogen-bonding patterns of the *syn* conformation of the β -isomer.

the carbonyl group and the glycoside nitrogen. Association between Fapy·dA and dG can be ascribed to a series of interactions similar to those characterized in a duplex that contains OA:dG base pairs.^[9] There are more base-pairing

schemes for Fapy·dA than for OA because of the greater degrees of freedom that can be attributed to the cleavage of the imidazole ring, as well as the existence of the lesion as an anomeric mixture.^[12]

Oligonucleotides that contain single diastereomers of non-epimerizable analogues of Fapy·dA, α -1, β -1 were prepared in order to probe the role of individual anomers in the above observations.^[4] Molecular mechanics calculations with the



Cerius2 program indicate that replacement of the glycoside amine with a methylene group does not significantly alter the minimum energy structure (data not shown). The incorporation of thymidine opposite α -1 and β -1 is impaired approximately tenfold relative to templates that contain Fapy·dA (Table 3). However, internal comparisons of the frequency of insertion (F_{rel}) of the four native nucleotides opposite β -1 reveal a remarkably similar pattern to that observed with the template that contains Fapy·dA (Table 3). In contrast, α -1 exhibits a much higher preference (F_{rel}) for incorporating dA, dG, and especially dC relative to T. These data suggest that β -1 is a more realistic mimic of Fapy·dA and that the glycoside nitrogen atom in the lesion is not involved in specific interactions.

In conclusion, experiments on oligonucleotides that contain Fapy·dA and configurationally stable analogues incorporated at defined sites enabled us to determine that this DNA lesion directs the misincorporation of dA translesionally. The conclusions drawn from these studies are different to those

Table 3. Kinetic parameters of nucleotide insertion opposite α -1 and β -1.

3'-d(T G G T A C C C T G C A T G C T G X G T C T C G C A A C T T G C G G A) 5'-d(A C C A T G G G A C G T A C G A C						
Klenow exo - dNTP						
3'-d(T G G T A C C C T G C A T G C T G X G T C T C G C A A C T T G C G G A) 5'-d(A C C A T G G G A C G T A C G A C N						
X	dNTP	K_{m} [μM]	V_{max} [% min ⁻¹]	$F_{\text{ins}}^{\text{[a]}}$	$F_{\text{rel}}^{\text{[b]}}$	
A	T	0.04	8.2	1.0	–	
A	A	125.8	49.9	1.8×10^{-3}	–	
A	G	58.8	11.6	1.0×10^{-3}	–	
A	C	56.3	2.6	2.7×10^{-3}	–	
β -1	T	0.90	5.5	2.7×10^{-2}	1.0	
β -1	A	321.8	55.0	7.8×10^{-4}	2.9×10^{-2}	
β -1	G	74.9	2.6	1.5×10^{-4}	5.6×10^{-3}	
β -1	C	96.0	1.7	7.8×10^{-5}	2.9×10^{-3}	
α -1	T	6.3	29.3	2.0×10^{-2}	1.0	
α -1	A	83.5	17.1	9.1×10^{-4}	4.6×10^{-2}	
α -1	G	39.9	2.7	3.7×10^{-4}	1.9×10^{-2}	
α -1	C	29.6	21.9	3.3×10^{-3}	0.17	

[a] $F_{\text{ins}} = (V_{\text{max}}/K_{\text{m}}, X = A, \text{dNTP} = T)/(V_{\text{max}}/K_{\text{m}}, X = A, \alpha\text{-1, or } \beta\text{-1, dNTP} = T, A, G, \text{ or } C)$. [b] $F_{\text{rel}} = (V_{\text{max}}/K_{\text{m}}, X = \alpha\text{-1 or } \beta\text{-1, dNTP} = T)/(V_{\text{max}}/K_{\text{m}}, X = \alpha\text{-1 or } \beta\text{-1, dNTP} = T, A, G, \text{ or } C)$.

from previous experiments in which Fapy·dA was randomly produced in DNA.^[5] Moreover, this investigation provides the first data that suggest that Fapy·dA may be a more potent premutagenic lesion than the chemically related OA. The significance of these in vitro experiments is magnified by the observation that Fapy·dA is produced in higher yield than OA.^[2c]

Experimental Section

Enzyme Kinetics: The appropriate primer (25 pmol) was labeled at its 5'-terminus with ³²P. The labeled primer was annealed to the appropriate template (375 pmol) and unlabeled primer (225 pmol) in ST buffer (20 mM Tris, pH 7.5; 100 mM NaCl) for 5 min at 90 °C (60 °C for Fapy·dA and its control duplex), and slowly cooled to room temperature. The duplexes were purified from excess [γ -³²P]ATP by passing through a G-25 Sephadex spin column equilibrated with ST buffer. The final concentration of the duplex was 3.13 μ M. Reactions were carried out by mixing a 2 $\times$ duplex-enzyme cocktail (5 μ L) to a 2 $\times$ dNTP solution (5 μ L). The reactions were run for a set period of time and quenched with 20 μ L of 95% formamide loading buffer containing 20 mM EDTA. The samples were denatured (90 °C for 3 min and cooled immediately to 0 °C), subjected to 20% denaturing PAGE, and analyzed on a Storm 820 phosphorimager equipped with Imagequant version 3.3 software. Kinetic parameters were calculated by using a Hanes–Woolf plot. All values are the average of at least three independent experiments. The 2 $\times$ duplex-enzyme cocktail consisted of duplex DNA (100 nM), Klenow exo⁻ (20 nM), and BSA (0.2 μ g μ L⁻¹) in 2 $\times$ Klenow buffer (20 mM Tris, pH 7.5, 10 mM MgCl₂, 15 mM DTT). Klenow was pretreated with inorganic pyrophosphatase (0.2 U per unit of enzyme) at room temperature for 10 min before adding the duplex. The 2 $\times$ duplex-enzyme cocktail was incubated for 5 min at room temperature. The 2 $\times$ dNTP solutions were made by diluting 100 mM stock solutions with the appropriate volume of water and stored at 4 °C. The concentrations of dNTP and reaction times were chosen such that the total amount of extension did not exceed 20%.^[10]

UV–Melting Experiments: Samples (total volume = 300 μ L) contained a 1:1 ratio of complementary oligodeoxynucleotides. Duplex concentrations ranged from 1 to 10 μ M. Solutions were prepared by the addition of appropriate volumes of stock solutions of the two complementary oligodeoxynucleotides to 150 μ L of 2 $\times$ PIPES (1,4-piperazine bis-(ethanesulfonate) sesquisodium salt) buffer (20 mM PIPES (pH 7.0), 20 mM MgCl₂, 200 mM NaCl), followed by dilution with distilled, deionized water to a volume of 300 μ L. The complementary oligodeoxynucleotides were hybridized by heating the samples to 60 °C, followed by slow cooling over 2–3 h to room temperature. Melting studies were carried out in 1-cm pathlength quartz cells. Absorbance was monitored while the temperature was ramped at a rate of 0.5 °C min⁻¹ from 25 to 75 °C. Melting temperatures were calculated by a computer fit of the first derivative of absorbance with respect to 1/T.^[13] All reported values are the average of at least four measurements. As a result of the lability of Fapy·dA to heat,^[12] studies

were carried out to ensure that significant decomposition (deglycosylation) did not occur during the repetitive hybridization and melting cycles required to obtain the above data. Following completion of UV–melting experiments 2 pmol of the recovered DNA (Fapy·dA and control containing dA) were radiolabeled by polynucleotide T4 kinase using [γ -³²P]ATP and precipitated to remove the residual nucleotide triphosphate by using standard methods. Labeled DNA (0.4 pmol) was resuspended in NaOH (0.1 M, 10 μ L) and heated at 55 °C for 20 min. The reaction was cooled in an ice bath and neutralized with aqueous HCl. The samples were taken up in 95% formamide loading buffer, and analyzed as described above. Decomposition was 5% relative to the control. **Supporting Information Available:** Direct comparison of kinetic experiments on Fapy·dA and OA.

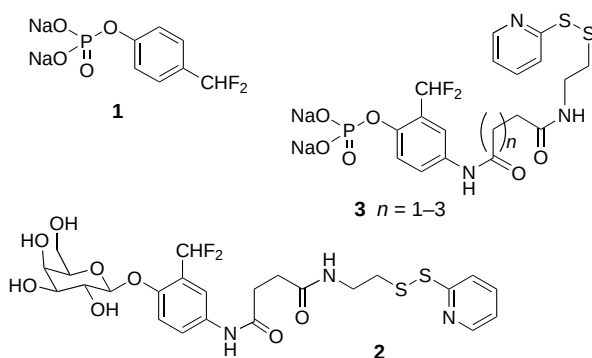
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Direct Screening for Phosphatase Activity by Turnover-Based Capture of Protein Catalysts**

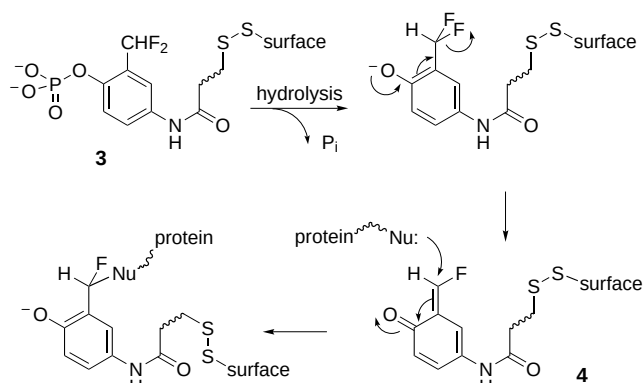
Jason R. Betley, Sandro Cesaro-Tadic, Abdelaziz Mekhalfia, James H. Rickard, Hazel Denham, Lynda J. Partridge, Andreas Plückthun,* and G. Michael Blackburn*

In studies towards the generation and identification of catalytic antibodies with phosphate monoesterase activity, we have developed a direct selection approach for covalent modification of catalysts founded on mechanism-based phosphatase inhibitors. It builds on the work of Halazy et al.^[1] in the use of *o*- and *p*-fluoromethylphenols to generate quinone methides as suicide substrates for glucosidases. Withers and co-workers conceived the use of 4-difluoromethylphenyl phosphate **1** as a suicide substrate for a human prostatic acid



phosphatase and a phosphotyrosine phosphatase,^[2] while Myers and Widlansky described the use of 4-monofluoromethylphenyl phosphate as a substrate.^[3] This strategy was later adapted by Janda et al.^[4] to pan a phage–Fab library of 9×10^3 members against the bovine serum albumin (BSA) conjugate of a reactive substrate **2** to select catalytic antibodies with galactosidase activity.

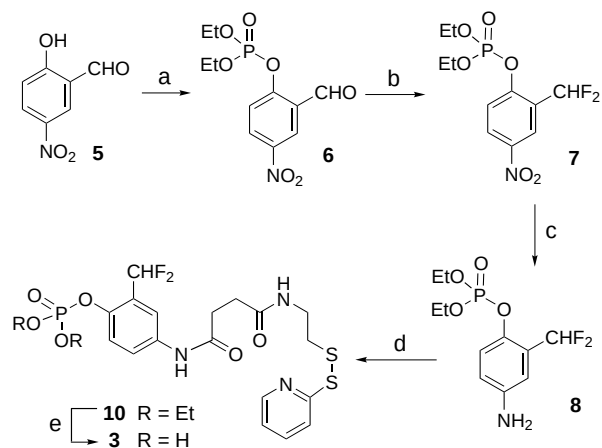
Our design of reagent **3** was developed in line with these examples (Scheme 1). The reactive 2-difluoromethylphenyl phosphate is linked by a variable spacer arm to a pyridyl-2'-disulfide. This enables the suicide substrate to be anchored to



Scheme 1. Mechanism of covalent binding of the suicide substrate **3** by formation of quinone methide **4**. Following phosphate hydrolysis, the protein catalyst becomes covalently attached to a carrier surface.

the surface of a solid support and also subsequent release of the trapped protein species by disulfide reduction with dithiothreitol. Covalent attachment to the protein results from the formation of a reactive quinone methide^[5] species **4** by elimination of fluoride after protein-catalyzed cleavage of the phosphate monoester bond. The catalytic protein (antibody or enzyme) then becomes covalently trapped as a consequence of the addition of a nucleophile to the quinone methide at or near the active site.

Substrate **3** was synthesized in six steps from 2-hydroxy-5-nitrobenzaldehyde (Scheme 2).^[6] Phosphorylation of phenol **5** led to the quantitative formation of phosphate triester **6**. Fluorination of aldehyde **6**,^[7] followed by quenching with ice



Scheme 2. Synthesis of **3**: a) $(\text{EtO})_2\text{POCl}$, Et_3N , CH_2Cl_2 ; b) Et_2NSF_3 (2.1 equiv), 0°C , 25 min; c) H_2 , Pd/C (10%); succinic anhydride, $i\text{Pr}_2\text{Et}$, CH_2Cl_2 ; d) 2-PySSCH₂CH₂NH₂ (**9**), EDC, CH_2Cl_2 ; e) Me_3SiBr , CH_2Cl_2 , then MeOH.

water, and purification by chromatography on silica gel gave **7**. The nitro group of **7** was catalytically hydrogenated without affecting the difluoromethyl group, and the resulting aniline **8** was treated with succinic anhydride. The succinyl hemiamide product was purified by means of silica-gel chromatography with a trace amount of acetic acid in the eluent. The thiol exchange moiety 2-PySSCH₂CH₂NH₂ (**9**), prepared from bis-2-aminoethyldisulfide dihydrochloride in two steps,^[8] was

[*] Prof. A. Plückthun, S. Cesaro-Tadic
Biochemisches Institut der Universität Zürich
Winterthurerstrasse 190, 8057 Zürich (Switzerland)
Fax: (+41) 1-635-5712
E-mail: plueckthun@biocfebs.unizh.ch

Prof. G. M. Blackburn, J. R. Betley, A. Mekhalfia, J. H. Rickard
Krebs Institute, Department of Chemistry
University of Sheffield
Sheffield, S3 7HF (UK)
Fax: (+44) 1142-738-673
E-mail: g.m.blackburn@sheffield.ac.uk
H. Denham, Dr. L. J. Partridge
Department of Molecular Biology and Biotechnology
University of Sheffield
Western Bank, Sheffield, S10 2TN (UK)

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coupled to **8** with EDC (*N*-ethyl-*N'*-dimethylaminopropylcarbodiimide) to give disulfide ester **10**. Finally, selective cleavage of the phosphate ethyl esters of **10** with bromotrimethylsilane^[9] gave the suicide substrate **3** ($n=1$).^[10] Two higher homologues of **3** were synthesized by using glutaric anhydride and adipic anhydride, respectively.^[11]

BSA was modified with Traut's reagent^[12] to convert some of the available ϵ -amino groups of surface lysine residues into thiols. Disulfide exchange with the suicide substrate **3** was undertaken immediately at 4 °C. The dephosphorylation of the BSA–**3** conjugate with alkaline phosphatase was determined by measuring the phosphate release with resorufin (P_iPer Phosphate Assay Kit, Molecular Probes). We found that all coupled substrate molecules were accessible to the enzyme and that the turnover compared well with that of the uncoupled substrate **3**. The suicide reagent **3**–BSA conjugate was immobilized onto the surface of standard Maxisorp ELISA plates by using various coating concentrations (ELISA = enzyme-linked immuno-sorbent assay). Alkaline phosphatase was added for various time periods followed by extensive washing in Tris-buffer pH 9.0 and 0.1M glycine–HCl pH 2.2. Any enzyme that was covalently trapped through the suicide reaction with **3** was detected by using a murine anti-alkaline phosphatase antibody and an anti-mouse-HRP secondary antibody (Sigma) with TMB substrate (3,3',5,5'-tetramethylbenzidine). Maximum linkage of alkaline phosphatase to the wells was obtained after incubation for 3 d^[13] (OD₄₅₀ = 1.5 with 10 $\mu\text{g mL}^{-1}$ BSA–**3** conjugate and 10 units of phosphatase per well).

In developing this selection tool, a major concern not fully resolved by earlier work is whether noncatalytic proteins can also be trapped. The results of Janda et al.^[4] for an antibody with galactosidase activity show multiple turnovers for the covalently captured protein catalyst. This implies that proteins may be trapped at amino acid residues *not* at the active site, conceivably not even in the same protein molecule. Furthermore, Raushel and co-workers have shown that the loss of catalytic activity resulted from the precipitation of a phosphate triesterase, caused by multiple modifications by a quinone methide species.^[14] To explore this possibility with **3**, alkaline phosphatase (10 units/well) was incubated with BSA–**3** for 3 d, and after appropriate washing steps, the *p*-nitrophenyl phosphate (3 mM in 10 mM diethanolamine buffer, pH 9.0, 50 μL /well) was added. The presence of trapped alkaline phosphatase was demonstrated by ELISA as described above.^[15] No formation of *p*-nitrophenol was observed, even after prolonged incubation.^[16] It follows that the enzyme has indeed been trapped either within the active site or sufficiently close to it, so that the bulky BSA conjugate occludes the active site. These results show that the suicide trapping of alkaline phosphatase by substrate **3** leads to the simultaneous immobilization and inactivation of the enzyme.

The ability of substrate **3** to serve as a turnover-based inhibitor for phosphatases was further investigated by means of BIAcore analysis.^[17] Inhibitor **3** was covalently immobilized on a BIAcore chip in a defined orientation by disulfide exchange. Upon injection, binding of alkaline phosphatase to the inhibitor resulted in an increase in the signal (Figure 1,

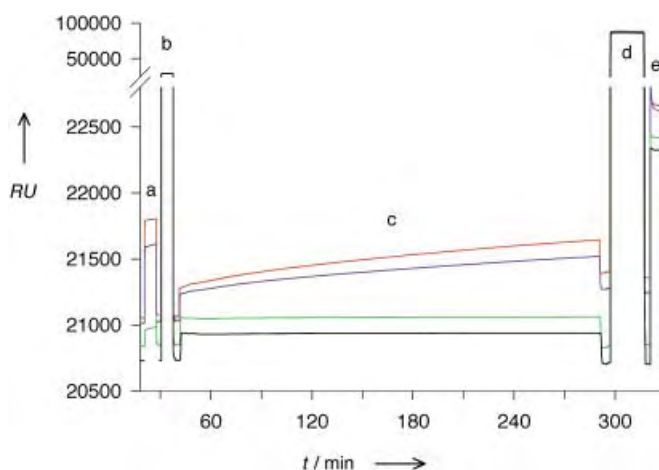


Figure 1. Plot showing turnover-based covalent interaction with enzyme at three concentrations of suicide substrate **3** ($n=2$). The sensorgram shows change of biosensor response units (RU) with time. Substrate **3** was immobilized on the thiol-activated chip surface by disulfide exchange (step a) with intensities of 5, 11, and 20 RU corresponding (according to its molecular mass) to about 0.1, 0.2, and 0.4 mM surface concentrations on flow cells 2 (green line), 3 (blue line) and 4 (red line), respectively. Flow cell 1 (black line) was an underivatized reference. Excess thiol was deactivated in all flow cells (step b) and alkaline phosphatase (0.1 μM) was injected for 4 h (step c). The enzyme was bound at intensities of 249 RU and 336 RU in flow cells 3 and 4, respectively. Noncovalently attached protein was finally washed off with guanidinium chloride (6M)(step d). The remaining signal intensities of 215 RU and 295 RU correspond to covalently trapped enzyme, which make up 86 % and 88 % of the entire bound phosphatase in flow cells 3 and 4, respectively. Enzyme binding at the lowest inhibitor concentration was very weak (11 RU). No binding of alkaline phosphatase to the reference surface in flow cell 1 was observed. The enzyme–inhibitor complex was finally released by disulfide bond cleavage (step e).

step c). More enzyme was bound at higher concentrations of the inhibitor on the surface. After injecting the alkaline phosphatase, a continuous flow of buffer was initiated. Only a small decrease in signal intensity was observed, which showed that little dissociation of phosphatase from the surface-bound complex had occurred. Most importantly, binding of the major part of the enzyme (>85 %) was not impaired even after extensive treatment with 6M guanidinium chloride. Clearly, the enzyme was covalently attached to the immobilized inhibitor.

The slow but progressive binding of alkaline phosphatase upon prolonged incubation for several hours in ELISA experiments or after prolonged flow of enzyme over the surface with immobilized inhibitor indicates a turnover-based interaction and is inconsistent with the rapid formation of a Michaelis complex of enzyme and substrate. Such binding would not be expected to give kinetically resolvable binding or dissociation traces in a BIAcore experiment, and at the protein concentrations used (small relative to K_M) its plateau height would be extremely small.^[18] The proportion of irreversibly bound enzyme was found to be dependent on the duration of the injection of alkaline phosphatase, which is consistent with the time dependence observed on microtitre plates. Unrelated proteins (e.g. BSA) did not activate the mechanistic trap nor did they bind at all to the suicide inhibitor. These results clearly show that inhibitor **3** traps the

phosphatase efficiently and selectively, thereby displaying the fundamental requirements for turnover-based enzyme inactivation.

We wondered whether a catalyst with low turnover rates, which would be expected to initially arise from selection experiments with a "first-generation" non-enzyme protein library (e.g. catalytic antibodies),^[19] can also be identified by means of this screening procedure. As a model for such a case, we investigated a mutant of alkaline phosphatase, S102A, which lacks the primary nucleophile at the active site. Even though the turnover rate for the S102A enzyme is about four orders of magnitude lower than for the wild-type, it is still substantially faster than the uncatalyzed reaction ($k_{\text{cat}}/k_{\text{uncat}} \cong 10^5$).^[20] Briefly, the mutant enzyme was injected in the BIAcore instrument in the same way as the wild-type enzyme to bind to the suicide substrate, and noncovalent bound protein was washed off with guanidinium chloride. More than 30% of the total bound enzyme remained after this step, demonstrating significant covalent coupling. The covalently coupled protein could be removed by reductive cleavage of the disulfide-containing linker that connects the suicide substrate to the surface. Thus, poorly active protein can still be identified by means of this turnover-based screening procedure. This strongly suggests that the rate of covalent inactivation depends on the successful reaction of a second nucleophile with the quinone methide rather than on the primary hydrolysis. However, under the same conditions, less enzyme is trapped than in the case of wildtype enzyme, thus suggesting that the suicide inhibitor may be potentially selective for catalytic efficiency. BSA does not show any covalent binding when used as a control in these reactions, excluding the possibility that the covalent binding might simply be a result of random reactivity of surface nucleophiles on the protein.

The synthesis and successful deployment of **3** is now being applied to the selection of catalysts from large protein libraries. Moreover, BIAcore analysis is demonstrated herein to represent a useful approach for the direct screening of library members and enables real-time analysis of the sequence of steps necessary for catalyst selection from a library of proteins. The relative advantages of *o*-trifluoro, *o*-difluoro, and *o*-monofluoromethylphenyl phosphate suicide substrates^[11] are currently under investigation.

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The Inhibiting Influence of Aromatic Solvents on the Activity of Asymmetric Hydrogenations**

Detlef Heller,* Hans-Joachim Drexler, Anke Spannenberg, Barbara Heller, Jingsong You, and Wolfgang Baumann*

Dedicated to Franz Hein (1892–1976)

Complexes of ruthenium, iridium, and especially rhodium have been used in the homogeneously catalyzed asymmetric hydrogenation of prochiral olefins, ketones, and imines.^[1] Hydrogenations are usually carried out in simple alcohols, but aromatic solvents, water, or alcohol/aromatic solvent mixtures can also be used. It has been reported that aromatic solvents such as benzene can inhibit asymmetric hydrogenation.

[*] Priv.-Doz. Dr. D. Heller, Dr. W. Baumann, Dr. H.-J. Drexler, Dr. A. Spannenberg, Dr. B. Heller
Institut für Organische Katalyseforschung, Universität Rostock e.V.
Buchbinderstrasse 5/6, 18055 Rostock (Germany)
Fax: (+49) 381-46693-83
E-mail: detlef.heller@ifok.uni-rostock.de
wolfgang.baumann@ifok.uni-rostock.de

Dr. J. You
Department of Chemistry, Sichuan University
610064 Chengdu (China)

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

tion. For example, Burk et al. recently showed that the hydrogenation of ethyl α -benzoyloxycrotonate with the very active Et-DuPHOS–Rh system (Et-DuPHOS = 2',5',2'',5''-tetraethyl-1,2-bis(phospholanyl)benzene) does not work in benzene, whereas high selectivity and activity are observed in other solvents. The formation of inactive [Rh(Et-DuPHOS)(benzene)]⁺ complex, which was characterized by means of ³¹P NMR spectroscopy, was postulated to be the cause.^[2]

The stability of such Rh^I– η^6 -arene complexes with chelating bisphosphanes has already been reported by Halpern et al.^[3] To our knowledge, only one crystal structure with a chiral bisphosphane is described: the benzene complex of (1*R*,2*R*)-*trans*-1,2-bis((diphenylphosphanyl)methyl)cyclobutane rhodium(I).^[4]

Bargon and co-workers used the PHIP method (PHIP = *para*-hydrogen-induced polarization) to investigate arene complexes of styrene derivatives.^[5] Likewise, Gridnev, Imamoto, and co-workers provided NMR spectroscopic evidence for the formation of Rh–arene complexes after the hydrogenation of phenyl-substituted enamides, preferably at lower temperatures.^[6] Herein we report detailed spectroscopic and kinetic investigations and quantitatively describe the inhibiting influence of η^6 -arene–Rh^I complexes on catalytic activity, for example, in the homogeneously catalyzed asymmetric hydrogenation. The crystal structures of arene complexes [Rh((*R,R*)-Et-DuPHOS)(benzene)]BF₄ (**1**) and [Rh((*S,S*)-Me-DuPHOS)(toluene)]BF₄ (**2**) are presented.

The addition of benzene or toluene (0.2 mL) to a solution of either [Rh(Et-DuPHOS)(MeOH)₂]BF₄ (**3**) or [Rh(Me-DuPHOS)(MeOH)₂]BF₄ (**4**)^[7] (0.01 mmol) in methanol (0.8 mL) already leads quantitatively to the corresponding arene complexes **1** and **2**, respectively. The formation of **1** and **2** was unequivocally confirmed by means of ³¹P or ¹⁰³Rh NMR spectroscopy (Table 1). The molecular structures are shown in Figure 1.^[8]

Although the ³¹P NMR data of the arene and of the methanol complexes are very similar (Table 1), the two complexes can be distinguished by means of ¹⁰³Rh NMR

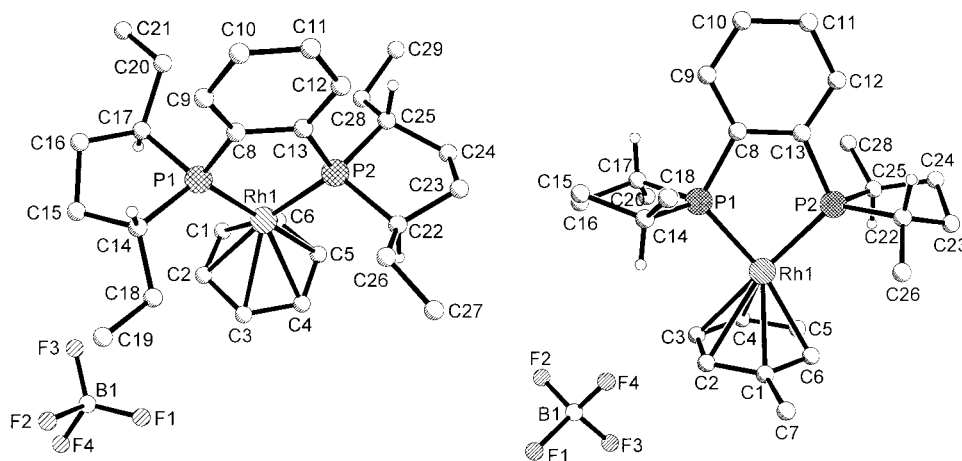


Figure 1. Molecular structures of **1** (left) and **2** (right) in the crystal (only hydrogen atoms at the asymmetric carbon atoms are represented). For disordered toluene, the atoms with highest probability of occupation (60 %) are shown. Selected bond lengths (Å) and angles (°) for **1/2**: Rh1–P1 2.211(2)/2.212(3), Rh1–P2 2.213(2)/2.214(3); P1–Rh1–P2 84.54(7)/84.88(10).

spectroscopy (Table 1).^[9] The signals for the arene complexes are clearly shifted upfield, and the established dependence of the rhodium shift on the size of the chelate ring is observed.^[10] The ¹H and ¹³C NMR spectra unambiguously confirm the presence of π -arene complexes. The signals for the coordinated benzene ring in **1** are shifted by –0.75 ppm in the ¹H NMR spectrum and by –27.8 ppm in the ¹³C NMR spectrum. A coupling constant of 2 Hz was found for ¹J(¹³C,¹⁰³Rh), and the observed ¹J(¹³C,¹H) value of 174 Hz is typical for π -arene complexes.^[11] Although a scalar ¹H,¹⁰³Rh coupling could not be resolved in the ¹H NMR signals of the coordinated arenes, its existence follows from the observation of crosspeaks in ¹H,¹⁰³Rh-HMOC experiments (HMOC = heteronuclear multiple quantum coherence), particularly for the methyl groups of π -coordinated toluene or xylene.

The stability of η^6 -arene complexes must be considered in asymmetric hydrogenations. The formation of stable Rh– π -arene complexes in the presence of aromatic solvents means that the rhodium catalyst is only partly available for the actual catalytic process.^[12]

The hydrogenation of dimethyl itaconate (**5**) with [Rh(Ph- β -glup-OH)(MeOH)₂]BF₄ (**6**)^[7c] (Ph- β -glup-OH = phenyl-2,3-bis(*O*-diphenylphosphanyl)- β -D-glucopyranoside) is a pseudo-first-order reaction in methanol. Mechanistically,^[13] this means that during the asymmetric hydrogenation, the equilibrium (solvent complex/prochiral olefin $\rightleftharpoons$ diastereomeric substrate complexes) is shifted toward the solvent complex. This is proven by UV/Vis spectroscopy.^[14] For such systems characterized by the low stability of the substrate complexes, it is to be expected that already small amounts of arene derivatives in the solvent (usually alcohol) lead to a decrease in the activity. Essentially, only the weakly coordinating solvent (present in a large excess) and the strongly coordinating arene derivative compete for the rhodium atom to form stable complexes. Thus, the addition of toluene (0.28 mmol, 0.03 mL) to a solution of **6** (0.02 mmol) and **5** (1.0 mmol) in methanol (15.0 mL) causes a reproducible decrease in the activity (Figure 2). It follows from the ratio of

Table 1. ³¹P and ¹⁰³Rh NMR data for solvent-stabilized cations of the type [Rh(P–P)(solvent)]BF₄ in [D₄]methanol at 298 K.^[a]

Chelate ligand	Solvent	$\delta(^{31}\text{P})$	$^1J(^{31}\text{P},^{103}\text{Rh})$ [Hz]	$\delta(^{103}\text{Rh})$
Et-DuPHOS	η^6 -benzene	93.0	202	–1116
	methanol	95.7	205	–149
DIPAMP	η^6 -benzene	72.2	207	–1006
	η^6 - <i>p</i> -xylene	75.7	207	–956
	methanol	81.2	208	–38
Ph- β -glup-OH	η^6 -toluene	136.4, 134.8	228, 228	–762
	methanol	147.6, 142.9	229, 226	–28

[a] Further data and experimental details are to be found in the Supporting Information.

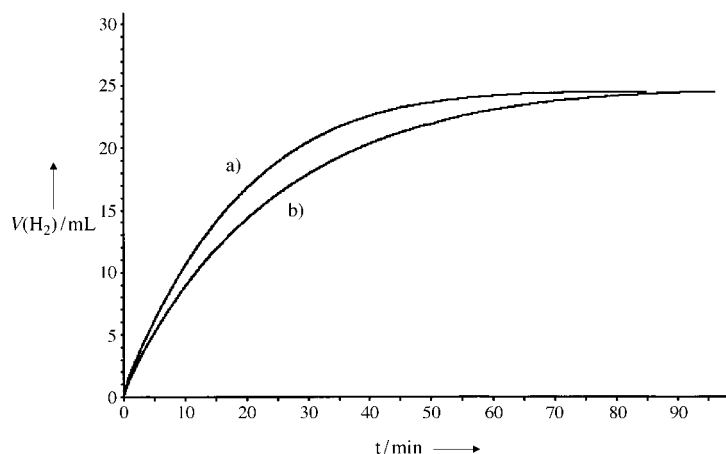


Figure 2. Hydrogenation of **5** in a) pure methanol ($k=0.055 \text{ min}^{-1}$) and b) after the addition of 0.28 mmol toluene ($k=0.041 \text{ min}^{-1}$); molar ratios: methanol/toluene 1320:1, toluene/Rh 14:1; reaction conditions: **6** (0.02 mmol), **5** (1.0 mmol), 1 bar total pressure, methanol (15.0 mL), 25.0°C .

the rate constants for the pseudo-first-order reaction that despite the clear excess of methanol (molar ratio methanol/toluene 1320:1), already 25 % of the catalyst for the asymmetric hydrogenation is blocked by the arene derivative. This finding from the quantitative analysis of the hydrogenation curve can be confirmed by NMR spectroscopy. A batch that contained the quantities specified in the legend of Figure 2 in only 1 mL of $[\text{D}_4]$ methanol (methanol/toluene 88:1) gave a methanol/toluene complex ratio of 3.5 (^{31}P NMR at 298 K), which agrees well with the value obtained from the kinetic investigation (2.93).

Hydrogenations of prochiral olefins, which form more stable rhodium complexes, can also be slowed down substantially by adding small amounts of aromatic compounds. The hydrogenation of methyl (*Z*)- β -(*N*-acetyl)-aminocrotonate (**7**), a model compound for the asymmetric hydrogenation of β -dehydroamino acids^[15] with $[\text{Rh}(\text{dipamp})(\text{MeOH})_2]\text{BF}_4$ (DIPAMP = 1,2-ethylenebis[(2-methoxyphenyl)phenylphosphane]) occurs in the saturation region of the underlying Michaelis–Menten kinetics (Figure 3a). The maximum rate (pseudo-zero-order reaction) does not depend on the concentration of the substrate (in the investigated substrate/catalyst range from 100:1 to 700:1). In such cases, the equilibrium (solvent complex/prochiral olefin $\rightleftharpoons$ diastereomeric substrate complexes) is shifted far toward the substrate complexes, as a result of the large stability constants. In this case, only the prochiral olefin and an arene derivative compete for the rhodium center, in contrast to hydrogenations with substrate complexes of low stability (see above). The addition of only 0.28 or 0.57 mmol *p*-xylene to a solution of **8** (0.01 mmol) and **7** (1.0 mmol) in methanol (15.0 mL) leads to a clearly diminished activity (Figure 3b, c). The enantioselectivity does not change within experimental errors. Interestingly, the hydrogenation is no longer a pseudo-zero-order reaction. However, if one considers that the concentration of the prochiral olefin decreases with increasing conversion and that the concentration of the aromatic compound remains constant, it

is clear that the proportion of blocking arene complex increases with increasing substrate conversion, and thus the activity decreases continuously. The amount of blocking *p*-xylene complex at the beginning of the hydrogenation (23 % or 53 %) can be determined from the ratio of the initial rates, or by means of ^{31}P NMR spectroscopy, which gave values of 25 % or 50 %. This is substantiated by the ^{103}Rh NMR shift for the species present beside the substrate complex (Figure 4).

Importantly, asymmetric hydrogenations can also be carried out in aromatic solvents. Eventually, the concentrations and stability constants of all compounds present in solution determine the extent of the decrease in activity.

The practical relevance of these results is finally demonstrated in an example. The hydrogenation of **7** with the Me-DuPHOS system in toluene as solvent (ambient temperature, 20 bar H_2) for 24 hours gives rise to the product with an *ee* value of 64 %.^[15] When methanol as solvent and **4** are used,

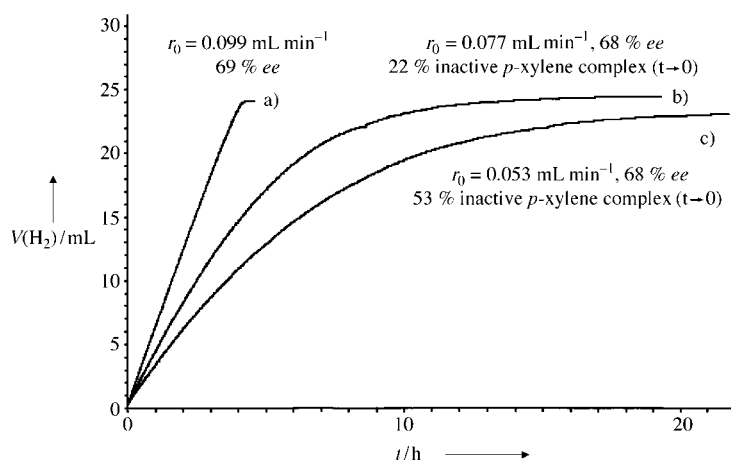


Figure 3. Hydrogenation of **7** in a) pure methanol and after the addition of b) *p*-xylene (0.28) or c) *p*-xylene (0.57 mmol); molar ratios: methanol/*p*-xylene 1323:1 (b), 650:1 (c); reaction conditions: **8** (0.01 mmol), prochiral olefin (1.0 mmol), methanol (15.0 mL), 1 bar total pressure, 25.0°C ; r_0 = initial rate.

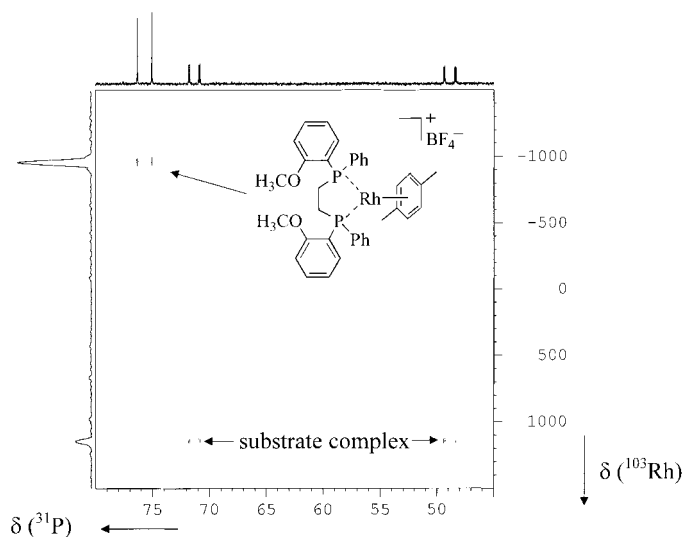


Figure 4. ^{31}P , ^{103}Rh -HMQC spectrum of a solution of **8** (0.01 mmol) in methanol, which was treated with **7** (1 mmol) and *p*-xylene (0.57 mmol); molar ratio of xylene complex/substrate complex = 1.0; the chemical shifts of the Rh signals for the xylene complex and for the substrate complex are -956 and 1148 ppm, respectively.

the product is obtained with 87.8% after only 4 min of hydrogenation at normal pressure at 25 °C.^[16] The lower activity in toluene is a result of the “induction periods”^[7] as well as the formation of stable, blocking arene complexes, as we have now shown quantitatively.^[17]

In summary, we have shown that arene complexes of Rh^I can have an unexpectedly large influence on the activity of asymmetric hydrogenation reactions. A different interpretation is now possible for past investigations in which catalyst activities were determined in alcohol/aromatic solvent mixtures or in aromatic solvents.^[18] At the moment, we are examining whether the inhibiting effect can also be induced by P-ligands and by substrates with aromatic substituents, and whether it is also relevant for other Rh^I-catalyzed reactions, for example, hydroformylations.

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The Core Structure of TMC-95A Is a Promising Lead for Reversible Proteasome Inhibition**

Markus Kaiser, Michael Groll, Christian Renner, Robert Huber, and Luis Moroder*

The proteasome is an intracellular multicatalytic protease complex which in combination with the ubiquitin pathway plays a central role in major cellular processes, such as antigen presentation, cell proliferation and differentiation, and apoptosis.^[1] Proteolysis occurs in a barrel-shaped core structure known as 20S proteasome, which consists of four stacked rings arrayed in an $\alpha\beta\gamma\beta\gamma\alpha$ mode.^[2a] In eukaryotic proteasome three β -subunits of each β -ring are enzymatically active with an N-terminal threonine residue as the active nucleophile involved in proteolysis^[2b] with three more or less distinct substrate specificities, that is chymotrypsin-like (CL), trypsin-like (TL), and peptidyl-glutamyl-peptide hydrolase (PGPH) activities.^[3]

Because of the physiological role of proteasome in critical intracellular processes, this enzyme represents a promising target for drug development in inflammatory and autoimmune diseases as well as in tumor therapy.^[4] Correspondingly, great attention has recently been paid to the discovery of potent and selective proteasome inhibitors by structure-based design or natural product screening approaches. Most of the synthetic inhibitors consisting of peptide aldehydes, boronates, and vinylsulfones, as well as the natural products lactacystin and epoxymycins inhibit in a more or less selective manner the proteasome by reaction with the N-terminal threonine residue (for a recent review see ref. [5]). A notable exception is the highly selective and competitive proteasome inhibitor TMC-95A, which was isolated from the fermentation broth of *Apiospora montagnei* Sacc. TC 1093.^[6]

This cyclic peptide metabolite consists of L-tyrosine, L-asparagine, a highly oxidized L-tryptophane, and the (Z)-1-

[*] Prof. L. Moroder, Dipl.-Chem. M. Kaiser, Dr. C. Renner
AG Biorganische Chemie
Max-Planck Institut für Biochemie
Am Klopferspitz 18 A, 82152 Martinsried (Germany)
Fax: (+49) 89-8578-2847
E-mail: moroder@biochem.mpg.de
Dr. M. Groll, Prof. R. Huber
Abteilung Strukturforschung
Max-Planck Institut für Biochemie
Am Klopferspitz 18 A, 82152 Martinsried (Germany)

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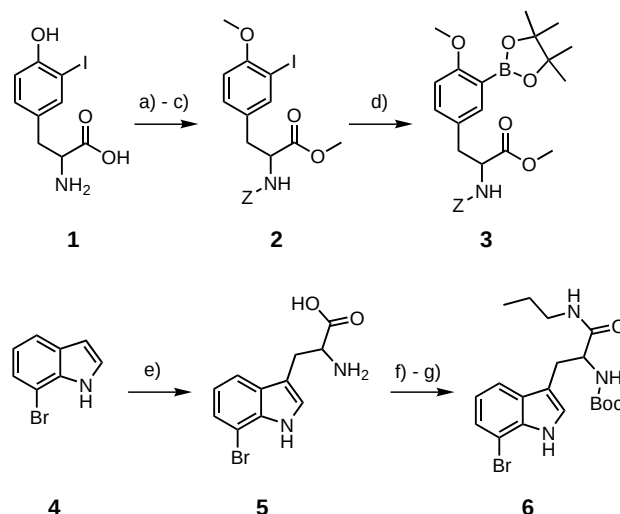
propenylamine and 3-methyloxopentanoic acid moieties with a phenyl/oxindole ring junction (structure A in Scheme 1).^[7] A similar biaryl moiety was so far encountered only in chloropeptin,^[8] complestatin,^[9] diazonamide,^[10] and the kistamincins.^[11] Because of the pharmacological interest of proteasome inhibition and the distinct phenol/oxindole system the synthesis of TMC-95A has attracted considerable interest.^[12]

X-ray structural analysis of the complex of TMC-95A with yeast proteasome clearly confirmed the noncovalent binding of this low molecular weight cyclic peptide, with a network of hydrogen bonds between the β -type extended peptide moiety and the main chain of the protein^[13] which contributes to the high affinity for all three active sites.^[6] From this crystal structure the minimum structural elements of TMC-95A for binding to the proteasome were derived (structure B in Scheme 1). To validate our working assumption we selected compound C (Scheme 1) as our first synthetic target; compound C contains a propylamide residue as R¹ for interaction with the S1 pocket of the active sites, and the side chain of asparagine, which is present in the natural product, as R³ for occupancy of the S3 pocket. All other modifications at the level of the core structure of TMC-95A were not expected to significantly affect the binding affinity for proteasome. The synthesis of this first TMC-95A analogue was accomplished and its inhibitory potency fully confirmed our working hypothesis.

The main difficulty in the synthesis of compound C was expected from cyclization to the constraint ring structure. Based on previous experiences reported for the synthesis of the chloropeptin ring,^[14] a first synthetic route by acid-catalyzed ring contraction of an 18-membered macrolactame precursor was attempted. This foresees a Suzuki cross-reaction for the preparation of the biaryl system followed by lactamization of the linear precursor. As meanwhile also reported by Estiarte et al.,^[15] cyclization of the 18-membered precursor failed. Thus, the compound C was synthesized according Scheme 2 and 3 by formation of the "correct" biaryl junction at the level of the linear precursor followed by cyclization.

For this synthetic route 3-iodo-L-tyrosine was converted into the suitably protected derivative **2** which was then transformed to the aryl boronate **3** by the Miyaura–Suzuki reaction^[16] using bis(pinacolato)diboron, [PdCl₂(dppf)], and

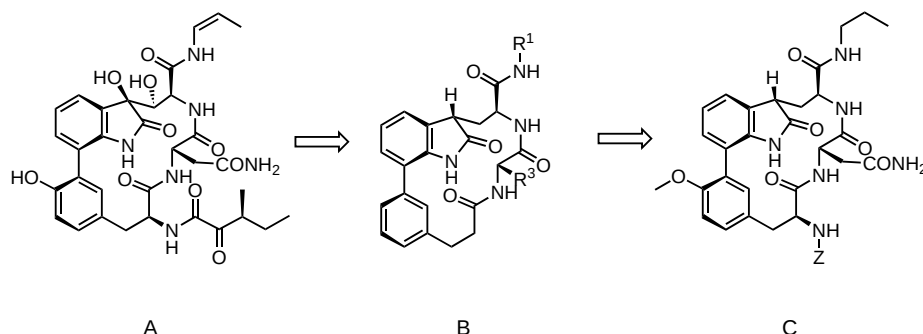
KOAc (Scheme 2). 7-Bromo-L-tryptophane was produced from 7-bromoindole and L-serine by the use of tryptophan synthetase following essentially known protocols^[17] and then



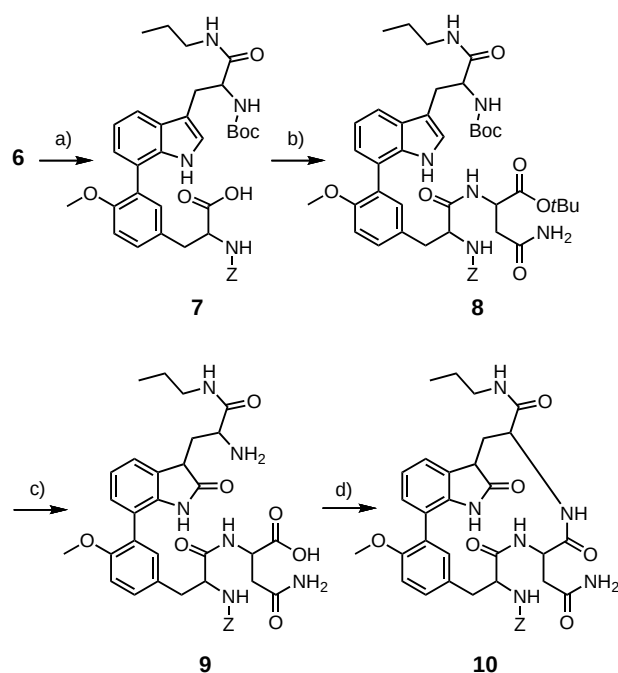
Scheme 2. Synthesis of **3** and **6**: a) SOCl₂, MeOH; b) Z-OSu; c) K₂CO₃ (10 equiv), MeI (5 equiv); d) B₂O₄C₁₂H₂₄ (1.1 equiv), [Pd(dppf)Cl₂]·CH₂Cl₂ (5 mol %), KOAc (3 equiv); e) L-serine, tryptophan-synthetase, PLP, 37 °C; f) Boc₂O; g) *n*PrNH₂, EDCI, HOBt. Z-OSu = *N*^α-(benzyloxycarbonyloxy)succinimide, dppf = Ph₂PC₃H₄FeC₃H₄PPh₂, PLP = pyridoxal 5'-phosphate, Boc = *tert*-butoxycarbonyl, EDCI = *N*'-(3-dimethylamino-propyl)-*N*-ethylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole, DME = dimethoxyethane.

converted into the related *N*^α-Boc propylamide derivative **6** (Scheme 2). The derivatives **3** and **6** were coupled under standard conditions of the Suzuki cross-reaction^[18] to generate the key intermediate **7** in 80% yield after flash chromatography (Scheme 3). Upon C-terminal extension of the peptide chain with the asparagine *tert*-butyl ester, the linear precursor **8** was oxidized at the indole moiety by standard procedures with DMSO/concentrated HCl^[19] (40% yield) prior to peptide cyclization with PyBOP/HOBt/DIEA. After HPLC purification the desired compound C (**10**) was isolated in about 40% yield as a homogeneous product (Scheme 3). NMR analysis confirmed the correct ring structure including the *S* configuration at the C3 atom of the oxindole.^[20] Apparently only this configuration allows cyclization of the precursor into the highly restricted ring. From distance and dihedral angle constraints derived from 2D NMR spectra a spatial structure of compound C was calculated which is superimposable to that of TMC-95A determined by X-ray analysis of its complex with the proteasome (Figure 1).

In the context of the structural analysis of the TMC-95A/yeast proteasome complex the natural product was found to inhibit the three proteolytic activities of yeast and



Scheme 1. Structure of TMC-95A (A), the minimal skeleton (B) for binding to the proteasome as derived from the X-ray structure of the TMC-95A/proteasome complex, and the analogue (C) with propylamide as R¹ and the side chain of asparagine as R³ residue. Compound C was synthesized for the validation of the design concept.



Scheme 3. Synthesis of **10**. a) **3** (1.1 equiv), [Pd(dppf)Cl₂] $\cdot$ CH₂Cl₂ (5 mol %), K₂CO₃ (3 equiv), DME/H₂O (7:1), 70 °C; b) H-Asn-OrtBu, EDCI, HOBT; c) DMSO (20 equiv), AcOH/HCl (4:1); d) PyBOP (4 equiv), HOBT (4 equiv), DIEA (6 equiv). PyBOP = benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, DIEA = diisopropylethylamine.

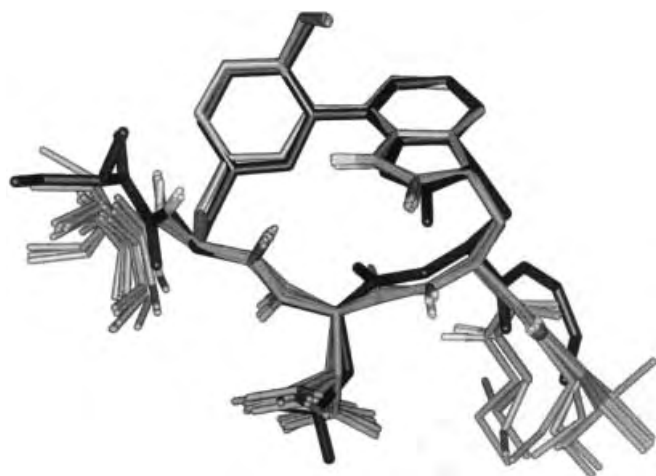


Figure 1. Conformation of compound **C** determined by NMR spectroscopy (20 lowest energy structures; gray) superimposed on the three-dimensional structure of TMC-95A as determined by X-ray analysis of its complex with yeast proteasome (black); for better visualization the N-terminal phenyl group is omitted.

human proteasome with similar potencies^[13] as previously reported for human proteasome.^[6] The inhibitory effects of compound **C** are reported in Table 1, and compared with those of TMC-95A and the calpain inhibitor **I**, that is Ac-Leu-Leu-Nle-H. Despite the difficult quantitative comparison of IC₅₀ values obtained with different proteasome preparations and assay conditions, the synthetic TMC-95A analogue was found to inhibit all three proteolytic activities more efficiently than the tripeptide aldehyde. Compared to the natural product, compound **C** retains almost full inhibition of the

Table 1. Inhibition of proteasome (IC₅₀ [μM]) by compound **C**, TMC-95A, and Ac-Leu-Leu-Nle-H in absence of SDS.^[21]

	CL activity	TL activity	PGPH activity
compound C	8.0 ^[a]	10.6 ^[a]	7.4 ^[a]
TMC-95A ^[6]	1.9 ^[b]	3.7 ^[b]	1.8 ^[b]
Ac-Leu-Leu-Nle-H	0.012 ^[b]	1.5 ^[b]	6.7 ^[b]
	35.4 ^[a]	142.5 ^[a]	88.0 ^[a]

[a] Yeast proteasome. [b] Human proteasome.

TL and PGPH activities, but it is significantly less potent against the CL activity. This may well be attributed to the exchange of the (*Z*)-1-propenylamide with the more flexible propylamide as P1 residue for occupancy of the specificity subsite S1 of the enzyme. Full retainment of affinity of compound **C** for the two other active sites of the proteasome confirms that the N-terminal acyl residue as well as the tyrosine hydroxy group are not critically involved in the interaction with the protein counterpart, whilst the biaryl moiety restricts the peptide backbone into the extended β-strand conformation for optimal hydrogen bonding to the active site clefts. The data also confirm that the degree of oxidation of the tryptophane residue can be reduced and that the oxindole group is sufficient for the additional hydrogen bond to the protein backbone to be established.

In conclusion, the inhibitory potencies of compound **C** confirm the correctness of our inhibitor design based on minimization of the TMC-95A skeleton, and clearly indicate that by optimization of the R¹ and R³ residues both selectivity and affinity for the three active sites may significantly be improved. These results also suggest that not all of the complex structural elements of the natural product are required for inhibition of proteasome, thus markedly facilitating the synthesis of TMC-95A related compounds.

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- [21] The IC₅₀ values for yeast and human 20S proteasome were determined at 37 °C in the absence of SDS using the fluorogenic substrates Suc-Leu-Leu-Val-Tyr-AMC, Bz-Thr-Val-Arg-AMC and Z-Leu-Leu-Glu-βNa to assay the CT, TL, and PGPH activities following essentially protocols reported previously (G. Loidl, H.-J. Musiol, M. Groll, R. Huber, L. Moroder, *J. Pept. Sci.* **2000**, *6*, 36–46).

P₂-Ligand Complexes as Building Blocks for the Formation of One-Dimensional Polymers**

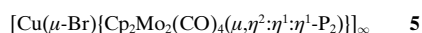
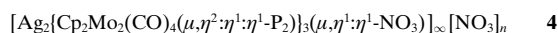
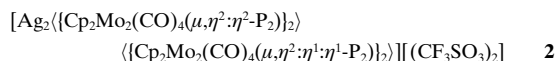
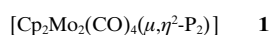
Junfeng Bai, Eva Leiner, and Manfred Scheer*

Dedicated to Professor Eckhard Herrmann on the occasion of his 65th birthday

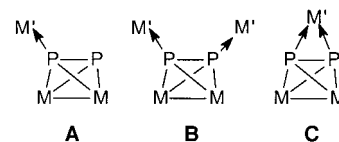
Self-organisation of discrete units to form supramolecular aggregates and networks of inorganic coordination compounds is a prominent field in contemporary chemistry.^[1] Within this field coordination polymers are of interest with regard to their physical, electronic, catalytic, and structural properties.^[2] Usual approaches in this area make use of N-donor containing ligands and heterocycles to connect different metal centers together. However, our goal in this field is to use P_n ligand complexes as connecting moieties between metal cations to form well-oriented assemblies as

well as one-dimensional (1D) and two-dimensional (2D) polymers.

The coordination chemistry of P_n ligand complexes^[3] towards cationic metal centers (excluding cationic organo-metallic complex moieties^[4]) has to date been limited to the use of cyclo-P₃ ligand complexes, such as [(triphos)M(η³-P₃)] (M = Co, Rh, or Ir; triphos = 1,1,1-tris(diphenylphosphanyl-methyl)ethane), which react with Cu^I, Ag^I, or Au^I to form metal-bridged dimers.^[5] In the reaction of the Co compound with CuBr, a multidecker complex of Co containing a (CuBr)₆ middle deck was obtained.^[6] To generate definite polymers, P₂-ligand complexes seem to be the starting material of choice. From our experience with the chromium complex [(CpCr(CO)₂)₂(μ,η²-P₂)]^[7] (Cp = C₅H₅) we know that this starting material readily undergoes fragmentation reactions;^[8] thus, we decided to use the more stable Mo analogue **1**.^[9] Herein we report the synthesis of a molecular cationic complex of Ag^I containing different and novel coordination modes of the P₂-ligand complex as well as the formation of the first 1D chain polymers of Ag^I and Cu^I containing P₂-ligand complexes.



The reaction of Ag(CF₃SO₃) with **1** in CH₃CN leads to the quantitative formation of **2**, in which the tetrahedral Mo₂P₂ ligand coordinates to two Ag(I) centers in a bridging as well as in a novel chelating coordination mode. Whereas the coordination of M₂P₂ tetrahedral complexes to one (type **A**) and two (type **B**) organometallic moieties is known, such as, in the type **B** situation where coordination to [Re(CO)₃Br] fragments forms a central six-membered ring moiety in complex **3**,^[10] the side-on coordination mode of an M₂P₂ complex at one metal center (type **C**), as found in complex **2**, is unique for a P₂-ligand complex.^[3]



If the counterions at the Ag^I centers are noncoordinating, complexes similar to **2** are obtained.^[11] However, we found a different coordination behavior if the counterion is incorporated into the coordination sphere of the Ag^I atom. Thus, the reaction of **1** with AgNO₃ leads to the quantitative formation of a novel polymeric Ag^I compound **4**, where one of the NO₃ counterions is now incorporated into the coordination sphere of the Ag^I atoms to form a waved 1D polymeric chain.

[*] Prof. Dr. M. Scheer, Dr. J. Bai, E. Leiner
Institut für Anorganische Chemie
Universität Karlsruhe
76128 Karlsruhe (Germany)
Fax: (+49) 721-608-7021
E-mail: mascheer@chemie.uni-karlsruhe.de

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Furthermore, the reaction of **1** with CuBr yields the novel linear 1D polymer **5**.

Complexes **2**, **4**, and **5** are red crystalline solids, which are stable under nitrogen and are sensitive to light in solution. They are insoluble in common solvents without decomposition; the exception being **2** which shows a slight solubility in CH₃CN. In the infrared (IR) spectra of all the obtained compounds, the CO stretching frequencies found are typical for terminal CO ligands. All the products have been examined by X-ray crystallography.^[12]

The molecular structure of **2** (Figure 1) consists of two Ag^I ions bridged by two Mo₂P₂ ligand complexes, which results in a central planar six-membered ring unit (the center of which

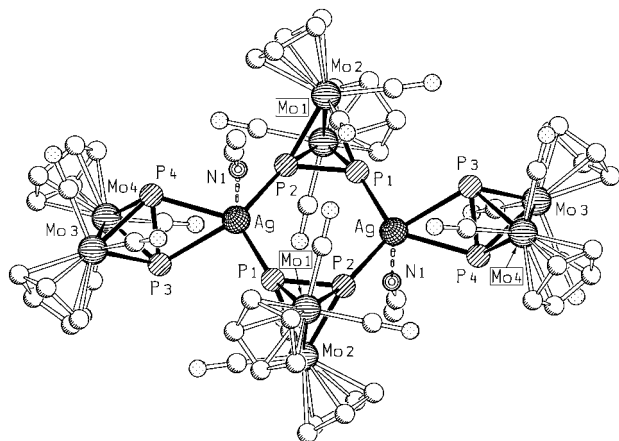


Figure 1. Molecular structure of the dianion from **2** (hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: Ag-P2 2.470(1), Ag-P1 2.489(1), Ag-P4 2.610(1), Ag-P3 2.727(2), P1-P2 2.098(2), P3-P4 2.137(2); P2-Ag-P4 108.32(8), P2-Ag-P1 120.28(8), P1-Ag-P4 131.04(8), P2-Ag-P3 130.25(8), P1-Ag-P3 98.96(8), P4-Ag-P3 47.45(7).

lies on the crystallographic inversion center); side-on coordinated Mo₂P₂ complexes complete the coordination sphere at the Ag^I ions. The [CF₃SO₃][−] counterions are completely separated from the cations. The dication possesses two additional CH₃CN molecules, which weakly interact with the Ag atoms (Ag⋯N = 2.598 Å), and this leads to a significantly distorted tetrahedral coordination environment at the Ag^I atoms. These CH₃CN molecules as well as the one

in the crystal lattice of **2** are easily lost if the compound is dried under vacuum. The bond lengths and angles of the bridging bidentate Mo₂P₂ fragments are similar to those found in other complexes, such as **3**,^[10] and, furthermore, they differ very little from those in the uncoordinated molecule **1**.^[9] The predominant difference between **2** and compounds **1** and **3** is the slightly longer bridging P–P bond (2.098(2) Å compared to 2.079(2) Å in **1** and 2.071(9) Å in **3**). More interesting is the comparison of the P–P bond lengths within **2**, where the chelating bond (2.137(2) Å) is much longer than the bridging one. The same trend is observed for the Ag–P distances, where the chelating Ag–P bonds (2.610(1) and 2.727(2) Å) are significantly longer than those of the central six-membered ring moiety (2.487(2) Å and 2.470(2) Å). However, in the ion [Ag(P₄)₂]⁺,^[13] where two P₄ units coordinate side-on at a Ag^I center, the Ag–P (2.536(2)–2.548(1) Å) as well as the P–P (2.328(2) and 2.330(2) Å) bond lengths are significantly longer than in the side-on bound (chelating) Mo₂P₂ moiety of **2**.

A view of the waved 1D chain structure of complex **4** is depicted in Figure 2. In **4** two different Ag^I atoms are each connected by bridging Mo₂P₂ units, to give two crystallographically distinct planar six-membered ring moieties (the center of each lies on a crystallographic inversion center), and are linked together by a third Mo₂P₂ unit and a bridging NO₃[−] ion, to form an additional seven-membered Ag₂NO₂P₂ ring system. The novel waved 1D chain of the cation is formed by alternating planar six-membered rings and novel seven-membered rings, in which each Ag^I center is in a distorted tetrahedral coordination environment. Whereas the bond lengths and angles of the six-membered ring, formed by the atoms Ag2, P5, and P6, are similar to those found for complex **2**, the second planar six-membered ring of **4**, formed by the atoms Ag1, P1, and P2, exhibits slightly lengthened P–P (2.097(2) Å, compared to 2.089(1) Å in **2**) and Ag–P (2.520(1) and 2.544(1) Å) bonds. This lengthening is caused by the influence of the different coordination modes of the bridging nitrate anion. Thus, the Ag2–O14 bond (2.526(3) Å), perpendicular to the plane of the nitrate anion, is longer than the Ag1–O13 bond (2.500(3) Å) which lies in the plane of the nitrate anion. Each of these bond lengths is in the range of reported Ag–O bonds (2.367–2.689 Å).^[14] Thus, shorter Ag–O bonds give longer Ag–P and P–P bonds in the six-

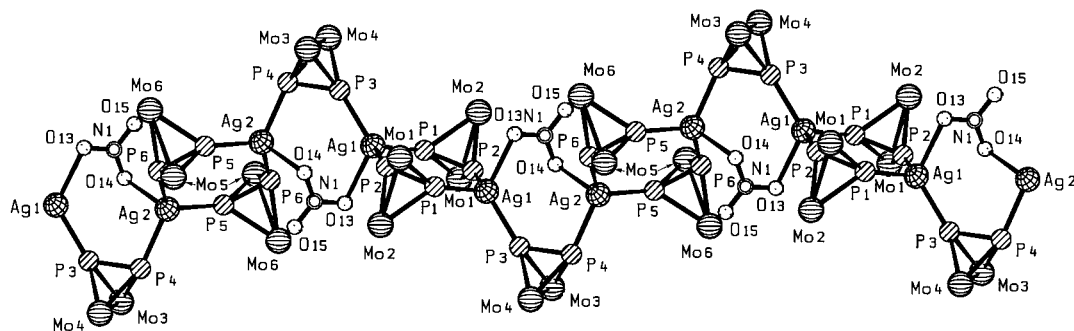


Figure 2. Section of the cationic polymer structure of **4** (the Cp and CO ligands are omitted for clarity). Selected bond lengths [Å] and angles [°]: P1-P2 2.097(2), P3-P4 2.099(2), P5-P6 2.089(1), Ag1-P3 2.495(1), Ag1-O13 2.500(3), Ag1-P1 2.520(1), Ag1-P2 2.544(1), Ag2-P6 2.478(1), Ag2-P4 2.492(1), Ag2-P5 2.498(1), Ag2-O14 2.526(3), P3-Ag1-O13 119.70(8), P3-Ag1-P1 111.35(3), O13-Ag1-P1 96.76(7), P3-Ag1-P2 119.31(4), O13-Ag1-P2 92.08(8), P1-Ag1-P2 114.43(4), P6-Ag2-P4 122.06(3), P6-Ag2-P5 119.49(4), P4-Ag2-P5 111.56(4), P6-Ag2-O14 97.61(6), P4-Ag2-O14 96.89(7), P5-Ag2-O14 101.99(7).

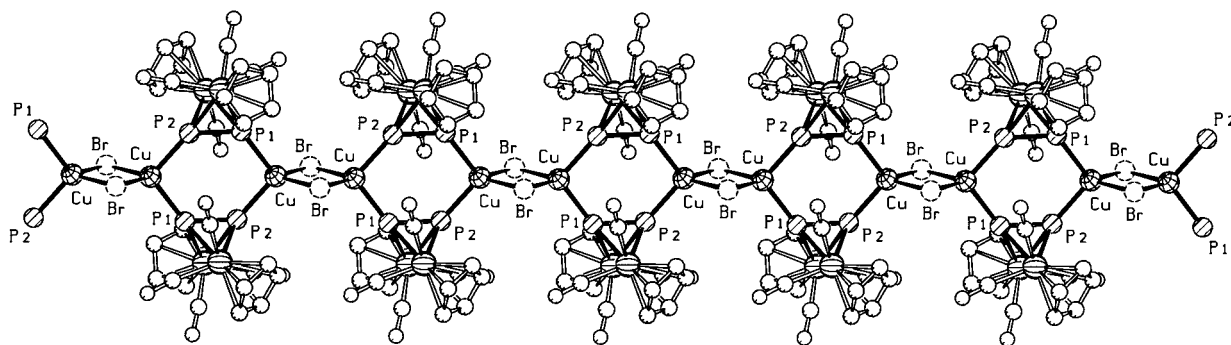


Figure 3. Section of the 1D polymer chain structure of **5** (hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: P1–P2 2.068(3), Cu–P 2.288(2), Cu–Br 2.465(1); P–Cu–P 102.02(10), P–P–Cu 128.99(5), Cu–Br–Cu 71.61(5), Br–Cu–Br 102.39(5).

membered rings and vice versa. Furthermore, the distance between the atoms O14 and Ag1 is 2.833(3) Å which indicates that there is a weak interaction between them.

In Figure 3 the linear 1D chain structure of **5** is depicted as consisting of planar six-membered Cu_2P_4 and four-membered Cu_2Br_2 rings, alternately arranged in an orthogonal manner. The coordination geometry at the Cu^{I} center is tetrahedral. The Cu^{I} atoms in **5** are symmetrically bound to the Br and P atoms. The P–P bond lengths in the P_2 units of **5** (2.079(1) Å) are similar to those in complex **3** (2.071(9) Å)^[10] and in the uncoordinated complex **1** (2.079(2) Å)^[9] but shorter than in the Ag^{I} complexes **2** and **4**. Furthermore, the bond lengths and angles of the bridging bidentate Mo_2P_2 fragments are similar to those found in the uncoordinated molecule **1**. The Cu–P bonds of **5** (2.288(1) and 2.297(1) Å) are slightly shorter than those in $\{[(\text{triphos})\text{CoP}_3]_2\text{Cu}\}\text{PF}_6 \cdot 2\text{THF}$ (2.360(2), 2.320(2), 2.303(2), and 2.329(2) Å). The Cu–Br bond of **5** (2.466(1) Å) is within the range displayed by the bromide-bridged complex $[\text{Cu}_2(\text{PPh}_3)_3\text{Br}_2]$ (2.370(2)–2.610(2) Å).^[15] The formation of **5** shows on the one hand the different coordination behavior of the Mo_2P_2 complex **1** with CuBr compared to the *cyclo*- P_3 complexes $[(\text{triphos})\text{M}(\eta^3\text{-P}_3)]$ (M = Co, Rh, or Ir) with CuBr.^[6] On the other hand there are similarities to the recently discovered use of copper(I) halides as matrices for the synthesis of novel ion-conducting materials.^[16]

In the ^{31}P NMR spectrum of complex **2** (CD_3CN) at room temperature, only one singlet is observed ($\delta = -69.0$). The chemical shift appears considerably upfield with respect to uncoordinated complex **1** ($\delta = -41.5$). Recording the ^{31}P NMR spectrum at the lowest possible temperature (-30°C)^[17] led to an upfield shift ($\Delta\delta = 14.7$ ppm) and to a significant broadening of the signal. Thus we assume for **2** in solution a fluxional process, where the coordination modes of the different Mo_2P_2 ligands are in fast exchange. Additional solid-state ^{31}P NMR studies to prove the different nature of the P atoms of **2** and also of **4** are in progress.

In conclusion, the results have shown that the Mo_2P_2 tetrahedral complex **1** seems to be an efficient starting material as a linker unit in supramolecular aggregates. Furthermore, it reveals that the influence of the counterion is crucial for the formation of a molecular or a polymeric structure. Thus, the use of noncoordinating counterions leads to molecular units, whereas the presence of coordinating counterions results in 1D polymeric structural frameworks.

Experimental Section

2: A solution of $\text{Ag}(\text{CF}_3\text{SO}_3)$ (25.7 mg, 0.1 mmol) in CH_3CN (25 mL) was added to a solution of **1** (99 mg, 0.2 mmol) in CH_3CN (15 mL) at 0°C . This mixture was stored at -30°C for two days and red crystals of **2** (93 mg, 0.15 mmol, 75 %) were formed. The product was collected by filtration and washed with CH_3CN (15 mL) and then dried under vacuum. IR (KBr): $\tilde{\nu} = 1992$ (vs), 1938 (vs), 1919 (vs) cm^{-1} (CO); $^{31}\text{P}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN , 25°C): $\delta = -69.0$ (s, $\omega_{1/2} = 100$ Hz); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_3CN , -30°C): $\delta = -83.7$ (s, $\omega_{1/2} = 200$ Hz); Elemental analysis (%) calcd for $\text{C}_{29}\text{H}_{20}\text{O}_{11}\text{P}_4\text{-SAgF}_3\text{Mo}_4$ (1249.05): C 27.89, H 1.61; found: C 28.33, H 1.82.

4: A solution of AgNO_3 (34 mg, 0.2 mmol) in CH_3CN (25 mL) was added to a solution of **1** (99 mg, 0.2 mmol) in CH_3CN (15 mL) at 0°C . This mixture was stored at -30°C for two days and red crystals of **4** (110 mg, 0.18 mmol, 90 %) were formed. The product was collected by filtration and washed with CH_3CN (15 mL) and then dried under vacuum. IR (KBr): $\tilde{\nu} = 2349$ (w) (CN), 2018 (w), 1970 (s), 1919 (vs), 1863 (m), 1837 (w) (CO), 1384 (vs) cm^{-1} (NO_3); Elemental analysis (%) calcd for $4 \cdot 3\text{CH}_3\text{CN}$: $\text{C}_{48}\text{H}_{39}\text{N}_5\text{O}_{18}\text{P}_6\text{Ag}_2\text{-Mo}_6$ (1951.08): C 29.55, N 3.59, H 2.01; found: C 29.36, N 3.09, H 2.30.

5: A solution of CuBr (57 mg, 0.4 mmol) in CH_3CN (10 mL) was added at room temperature to a solution of **1** (100 mg, 0.2 mmol) in CH_3CN (10 mL), and a red precipitate of **5** appeared instantly. Further stirring for 1 h at room temperature led to the complete formation of **5** (112 mg, 0.174 mmol, 87 %), which was collected by filtration, washed with CH_3CN (3×25 mL), and dried under vacuum. Single crystals of **5** were obtained by very slow diffusion of CH_3CN solutions of the starting materials. IR (KBr): $\tilde{\nu} = 2008$ (vs), 1962 (s), 1928 (vs), 1861 (s), 1834 (s) cm^{-1} (CO); Elemental analysis (%) calcd for $\text{C}_{14}\text{H}_{10}\text{BrCuMo}_2\text{O}_4\text{P}_2$ (639.51): C 26.29, H 1.58; found: C 26.69, H 1.42.

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Tetra- and Pentacyclopentadiene—Two New Donor-Substituted Ligands for Metal Complexes**

Ingo Emme, Stefan Redlich, Thomas Labahn, Jörg Magull, and Armin de Meijere*

Dedicated to Professor Oskar Glemser on the occasion of his 90th birthday

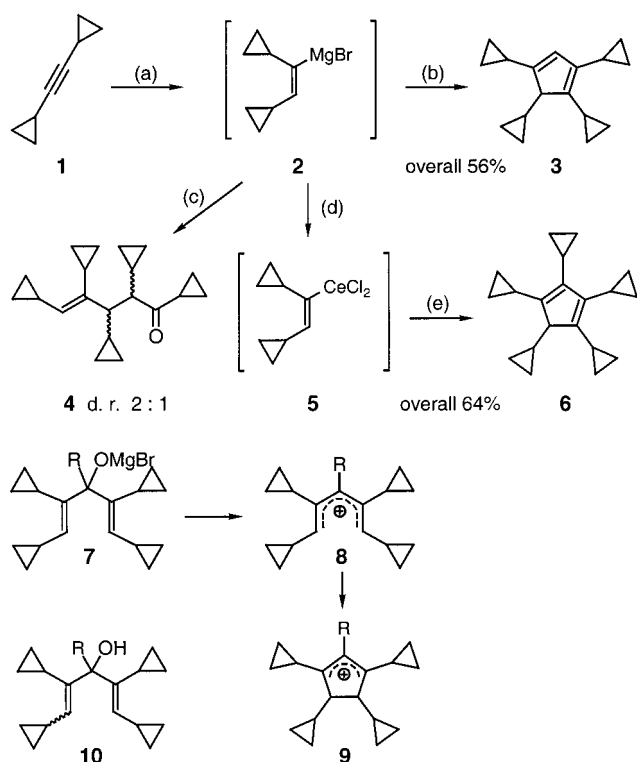
Ligand tuning undoubtedly is one of the most important tools to modify the properties of metal complexes, for example to enhance the catalytic activity and stereoselectivity in metal-catalyzed reactions. Both the electronic and steric factors play an important role in this context. Among the most frequently used ligands are cyclopentadiene and its substituted analogues.^[1] Although a great variety of substituted cyclopentadienes have been prepared, very little is known about cyclopropyl-substituted derivatives. Yet the cyclopropyl group has unique electronic properties^[2, 3] in that it is a particularly good donor for electron-deficient centers, and sterically it is closer to an ethyl than to an isopropyl group.^[4] We here report on the first synthesis of tetra- and pentacyclopentadiene^[5] and some of their metal complexes.

Applying the protocol of Sato et al. for the hydromagnesation of alkynes,^[6] the easily accessible dicyclopentadiene (**1**),^[7] by treatment with isobutylmagnesium bromide in the presence of titanocene dichloride (1 mol%) in diethyl ether, was transformed to 1,2-dicyclopentadienylmagnesium bromide (**2**) which, when added to a solution of *n*-butyl formate in tetrahydrofuran, gave 1,2,4,5-tetracyclopentadiene (**3**) right away in 56% yield (Scheme 1). The expected 1,2,4,5-tetracyclopentadiene-1,4-dien-3-ol (**10**, $\text{R} = \text{H}$) was isolated in poor yield along with an isomer and a lot of polymeric material only when the *n*-butyl formate was added to the solution of the Grignard reagent **2**. In fact, the dienol **10** could not be converted to the cyclopentadiene **3** under the conditions that have been established for the conversion of

[*] Prof. Dr. A. de Meijere, Dr. I. Emme, Dipl.-Chem. S. Redlich
Institut für Organische Chemie
Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-399475
E-mail: Armin.deMeijere@chemie.uni-goettingen.de
Dipl.-Chem. T. Labahn, Prof. Dr. J. Magull
Institut für Anorganische Chemie
Georg-August-Universität Göttingen
Tammannstrasse 4, 37077 Göttingen (Germany)

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



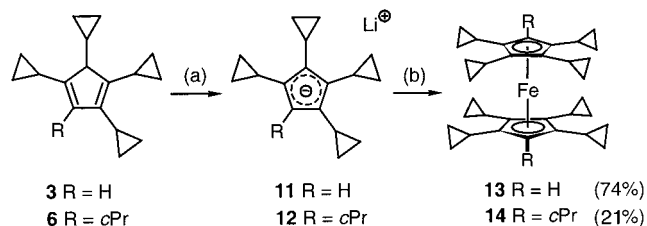
Scheme 1. a) $i\text{BuMgBr}$ (1 equiv), $[\text{Cp}_2\text{TiCl}_2]$ (1–2 mol %), Et_2O , 20°C , 30 min. b) Add inversely to HCO_2nBu (0.9 equiv) in THF, 20°C , 1 h. c) Add inversely to cPrCO_2Me in THF, 20°C , 1 h. d) Add inversely to a suspension of CeCl_3 (1.5 equiv) in THF, 20°C , 1 h. e) 1) Add cPrCO_2Me (0.48 equiv) in THF, 20°C , 1 h; 2) $\text{H}_2\text{O}/\text{HOAc}$ (6:1).

the corresponding tetramethyl-substituted pentadienol to tetramethylcyclopentadiene.^[8] Thus, **3** must have been formed from the magnesium alkoxide **7** ($\text{R} = \text{H}$) prior to hydrolysis. Owing to its drastically enhanced stability (by way of the four cyclopropyl substituents) the pentadienyl cation **8** ($\text{R} = \text{H}$) is probably formed from **7** ($\text{R} = \text{H}$) under the action of the Lewis acidic magnesium halide in the solution, and **8** then undergoes the well-known conrotatory 4π -electrocyclization.^[9] Subsequent deprotonation of the resulting cyclopentenyl cation **9** ($\text{R} = \text{H}$), which also enjoys enhanced stability due to its cyclopropyl substituents, leads to the cyclopentadiene **3**.

To access 1,2,3,4,5-pentacyclopentadiene (**6**), the obvious next experiment was to add the Grignard reagent **2** to methyl cyclopropanecarboxylate (Scheme 1). However, the only isolated product was the pentacyclopentadienone **4** (58% yield), which apparently was formed by 1,4-addition of the second molecule of **2** onto the first formed enone intermediate from cyclopropanecarboxylate and **2**. To prevent this reaction mode, the solution of **2** in diethyl ether was first combined with a slurry of cerium(III) chloride in tetrahydrofuran,^[10] then methyl cyclopropanecarboxylate was added at ambient temperature. After optimization of all parameters, work-up of this reaction mixture with aqueous acetic acid (6:1) gave the cyclopentadiene **6** in 64% yield.^[11] Thus, the pentacyclopentadienyl cation **8** ($\text{R} = \text{cPr}$) also must be formed easily and undergo cyclization to **9** ($\text{R} = \text{cPr}$) readily.

Upon treatment with an ethereal solution of methyllithium, both cyclopropyl-substituted cyclopentadienes **3** and **6** in

tetrahydrofuran were quantitatively deprotonated to the corresponding cyclopentadienides **11** and **12**, respectively (Scheme 2), which were characterized by their ^1H and ^{13}C NMR spectra (Table 1). Treatment of the solutions of **11** and **12** with solutions of iron(II) chloride in tetrahydrofuran yielded the 1,1',2,2',3,3',4,4'-octacyclopentadiene (**13**) (74%) and the decacyclopentadiene (**14**) (21%). After crystallization of **13** (from hexane) and **14** (from pentane/dichloromethane), the structures of both ferrocenes were established by X-ray crystal structure analysis (Figure 1).^[12]



Scheme 2. a) MeLi (1 equiv) in Et_2O , THF, -78 to -20°C , 45 min. b) Add to $\text{FeCl}_2 \cdot 2\text{THF}$ in THF, 0 to 20°C , reflux, 5 h.

Table 1. ^{13}C NMR spectroscopic data (δ_{TMS}) of various cyclopentadienyl anions and ferrocenes as well as oxidation potentials ($E_{1/2}$ versus SCE) of ferrocenes (see Scheme 2).

Entry	Compound	$\delta(^{13}\text{C})^{\text{[a]}}$ (Solvent)	$E_{1/2}^{\text{[b]}}$ [V]	Ref.
1	$\text{C}_5\text{H}_5\text{Li}$	103.2 ($[\text{D}_8]\text{THF}$)	–	[13]
2	$\text{C}_5\text{Me}_5\text{Na}$	105.1 ($[\text{D}_8]\text{THF}$)	–	[14]
3	$\text{C}_5(\text{iPr})_4\text{HNa}$	120.2 ($[\text{D}_8]\text{THF}$)	–	[15]
4	$\text{C}_5(\text{iPr})_5\text{Na}$	112.4 ($[\text{D}_8]\text{THF}$)	–	[16]
5	$\text{C}_5(\text{cPr})_4\text{HLi}$ 11	117.4, 116.2, 92.8 ($[\text{D}_8]\text{THF}$)	–	this work
6	$\text{C}_5(\text{cPr})_5\text{Li}$ 12	116.5 ($[\text{D}_8]\text{THF}$)	–	this work
7	$(\text{C}_5\text{H}_5)_2\text{Fe}$	68.2 (C_6D_6)	+ 0.48	[17]
8	$(\text{C}_5\text{Me}_5)_2\text{Fe}$	78.4 (C_6D_6)	– 0.07	[14]
9	$[\text{C}_5(\text{iPr})_4\text{H}]_2\text{Fe}^{\text{[c]}}$	92.3, 89.7, 59.4 (C_6D_6)	[d]	[15]
10	$[\text{C}_5(\text{cPr})_4\text{H}]_2\text{Fe}$ 13	87.3, 87.0, 62.9 (C_6D_6)	– 0.01	this work
11	$[\text{C}_5(\text{cPr})_5]_2\text{Fe}$ 14	85.1 (C_6D_6)	– 0.13	this work

[a] Only for the central five-membered ring. [b] Scan rate: 0.1 V s^{-1} ; $0.1 \text{ M } n\text{Bu}_4\text{NPF}_6$ in CH_2Cl_2 ; versus SCE; $E^0 \sim E_{1/2} = (E_{\text{PA}} + E_{\text{PC}})/2$. [c] Decaisopropylferrocene could not be prepared, as sodium penta-isopropylcyclopentadienide was oxidized to the persistent penta-isopropylcyclopentadienyl radical upon treatment with FeCl_2 .^[18] [d] Not reported.

Interestingly, none of the cyclopropyl substituents on the two parallel orientated cyclopentadienyl rings in **13** and **14** are in the proper bisected orientation in which they would donate electron density^[2, 3] to the central cyclopentadienide fragments. The dihedral angles, for example, in **14** alternate from closer to bisected to closer to perpendicular (39.8 , 70.7 , 20.1 , 63.4 , 61.1°), all cyclopropyl groups pointing away from the metal center. Of course, crystal packing effects may play an important role, and in solution the average orientation of all cyclopropyl groups may well be closer to the bisected conformation. The average distance between the iron and the cyclopentadienyl carbon atoms in **14** is slightly longer ($206.8(5) \text{ pm}$) than that in the parent ferrocene ($204(2) \text{ pm}$),^[19] and so is the average C–C bond length in the ring ($144.2(8)$ versus $140(2) \text{ pm}$).

To probe for the electronic properties of the new cyclopropyl-substituted ligands, the oxidation potentials of ferro-

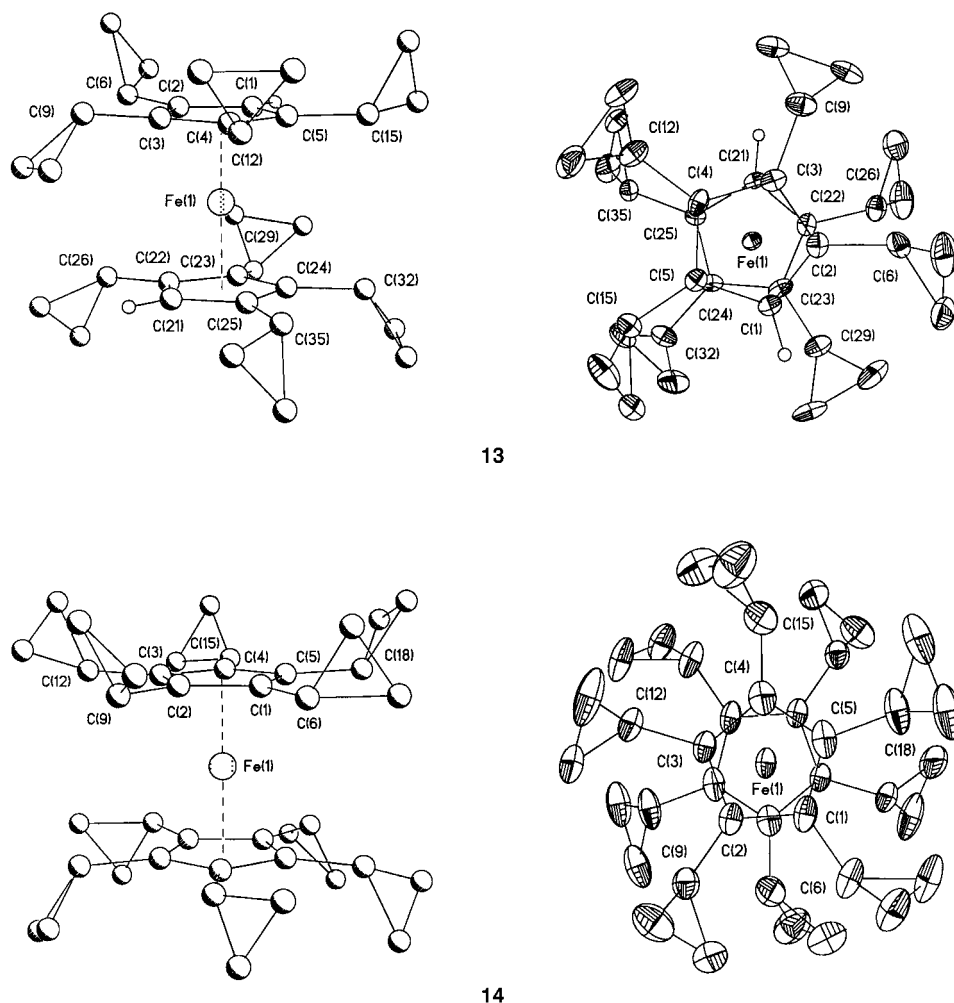


Figure 1. Structures of **13** and **14** in the crystal.^[12]

cenes **13** and **14** were determined by cyclic voltammetry. While this value for **13** of $E_{1/2} = -0.01$ V is slightly higher than that for decamethylferrocene ($E_{1/2} = -0.07$ V), the oxidation of **14** occurs at a slightly lower potential ($E_{1/2} = -0.13$ V). Both oxidations are fully reversible which indicates that the cyclopropyl groups in the ferrocenium ions stay intact.

In view of their easy accessibilities (one step each from dicyclopropylacetylene,^[7] three steps from commercially available starting materials,^[20] it is well conceivable that cyclopentadienes **3** and **6** with their fine-tuned steric demand and electronic features will establish themselves as new ligands in organometallic chemistry.

Experimental Section

6: Cerium(III) chloride heptahydrate (6.71 g, 18.0 mmol) was dried for 5 h at 180 °C (0.05 mbar). After cooling down to room temperature the anhydrous CeCl_3 was suspended in THF (150 mL) by stirring for 1 h. Meanwhile a solution of dicyclopropylethyne (**1**) (2.68 g, 25.2 mmol) and *i*BuMgBr in Et_2O (35.8 mL, 24.0 mmol, 0.67 M) was treated with $[\text{Cp}_2\text{TiCl}_2]$ (74.7 mg, 300 μmol , 1.25 mol %), stirred for 30 min at room temperature and was added to the CeCl_3 suspension. After 1 h at room temperature, the reaction mixture was treated with $c\text{PrCO}_2\text{Me}$ (1.22 g, 12.0 mmol) and was stirred for an additional 1 h at 20 °C, then aqueous acetic acid (6:1, 70 mL) was added. The phases were separated after 30 min, the organic layer was washed with

water (2×50 mL) and 1 M NaHCO_3 (2×50 mL), and the combined aqueous layers were extracted with pentane (2×50 mL), dried over MgSO_4 , and the solvents were removed in vacuo. Chromatography on silica gel (elution with pentane) yielded **6** (2.14 g; 64%, based on **1**; $R_f = 0.5$ in pentane) as a colorless oil. IR (film): $\tilde{\nu} = 3079$ (C-H), 3003 (C-H), 2869 (C-H), 1636 (C=C), 1457, 1427, 1264, 1021, 943, 889, 819 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3): $\delta = 0.20$ –0.85 (m, 21 H; $c\text{Pr-H}$), 1.42 (m, 2 H; $c\text{Pr-H}$), 1.55 (m, 2 H; $c\text{Pr-H}$), 1.84 (d, $^3J = 9.55$ Hz, 1 H; 5-H); ^{13}C NMR (62.9 MHz, CDCl_3 , DEPT): $\delta = 4.1$ (–, 2 C; $c\text{Pr-C}$), 6.1 (–, 2 C; $c\text{Pr-C}$), 6.2 (–, 2 C; $c\text{Pr-C}$), 6.5 (–, 2 C; $c\text{Pr-C}$), 7.8 (–, 2 C; $c\text{Pr-C}$), 8.8 (+, 2 C; $c\text{Pr-C}$), 9.8 (+, 2 C; $c\text{Pr-C}$), 12.5 (+, 1 C; $c\text{Pr-C}$), 58.5 (+, C-5), 142.2, 143.9 (C_{quat} , C-1(4), C-2(3)); MS (70 eV): m/z (%): 266 (100) [M^+], 237 (90) [$\text{M}^+ - \text{C}_2\text{H}_5$], 225 (75) [$\text{M}^+ - \text{C}_3\text{H}_5$], 209 (61), 195 (42), 181 (60), 167 (66), 155 (44), 141 (39), 128 (24), 115 (29), 91 (26), 41 (18) [C_3H_5^+]; elemental analysis (%) calcd for $\text{C}_{20}\text{H}_{26}$ (266.4): C 90.16, H 9.84; found: C 90.09, H 9.71.

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- [12] Crystal structure analyses: **13** (C₃₄H₄₂Fe): *Z* = 4, *M_r* = 506.56, crystal dimensions: 0.50 × 0.40 × 0.40 mm, monoclinic, space group *P*2₁, *a* = 876.8(2), *b* = 3494.8(7), *c* = 897.2(2) pm, β = 102.34(3)°, *V* = 2.6859(9) nm³, ρ_{calcd} = 1.253 Mg m⁻³, *F*(000) = 1088, λ = 71.073 pm, *T* = 133(2) K, $\mu(\text{MoK}\alpha)$ = 0.582 mm⁻¹, 2.32° ≤ 2 θ ≤ 25.02°; out of 33 365 collected reflections, 9498 are independent and were used for structure refinement of 632 parameters. The *R* values are *R*₁ = 0.0370 (*I* > 2 σ (*I*)) and *wR*₂ = 0.0716 (all data); min./max. residual electron density: −345/189 e nm⁻³. **14** (C₄₀H₅₀Fe): *Z* = 1, *M_r* = 586.65, crystal dimensions: 0.60 × 0.40 × 0.50 mm, triclinic, space group *P*1̄, *a* = 911.2(2), *b* = 982.6(2), *c* = 1043.6(2) pm, α = 117.56(1)°, β = 107.35(1)°, γ = 90.38(1)°, *V* = 0.7790(2) nm³, ρ_{calcd} = 1.251 Mg m⁻³, *F*(000) = 316, λ = 71.073 pm, *T* = 133(2) K, $\mu(\text{MoK}\alpha)$ = 0.511 mm⁻¹, 2.38° ≤ 2 θ ≤ 24.74°; out of 6373 collected reflections, 2606 are independent and were used for structure refinement of 175 parameters. The *R* values are *R*₁ = 0.0666 (*I* > 2 σ (*I*)) and *wR*₂ = 0.1926 (all data); min./max. residual electron density: −581/1142 e nm⁻³. CCDC-172568 (**13**) and CCDC-172569 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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Spinel Sialons**

Marcus Schwarz,* Andreas Zerr, Edwin Kroke,*
Gerhard Miehe, I-Wei Chen, Martin Heck,
Brunhilde Thybusch, Brent T. Poe, and Ralf Riedel

In the system Si–Al–O–N and related multinary systems a large variety of crystalline and vitreous phases is known. These so called sialons are of technological importance, especially for applications as structural ceramics.^[1] The term “classical sialons” refers to the solid solutions of Al₂O₃, (AlN), and Si₃N₄, known as β -sialons because of their close structural relationship to β -Si₃N₄.^[2] By analogy, α -sialons can be derived from α -Si₃N₄, but they also incorporate metal ions such as Li, Ca, and Y and most rare earth metals.^[1,2] These Si–Al–O–N systems have been extensively studied. Haviar et al. reported their behavior at high temperature (up to 1800 °C) and high pressure (up to 6 GPa).^[3]

Here we report the synthesis and structure determination of a high-pressure sialon phase with spinel structure (space group *Fd3m*) by conversion of β -Si₂AlON₃ at 13 GPa/1800 °C. Its hardness of 27.5 GPa significantly exceeds those of β - and α -sialons.

This work extends the recent discovery of binary spinel nitrides γ -E₃N₄ (E = Si, Ge, Sn),^[4] in which both octahedral and tetrahedral lattice sites are occupied by cations with a

[*] Dipl.-Ing. M. Schwarz, Dr. E. Kroke,^[+] Dr. A. Zerr,
Prof. Dr. R. Riedel
Fachgebiet Disperse Feststoffe
Fachbereich Material- und Geowissenschaften
Technische Universität Darmstadt
Petersenstraße 23, 64287 Darmstadt (Germany)
Fax: (+49) 6151-166346
E-mail: mrschw@tu-darmstadt.de
kroke@tu-darmstadt.de

Dr. G. Miehe
Fachgebiet Strukturforschung
Fachbereich Material- und Geowissenschaften
Technische Universität Darmstadt (Germany)

Dr. M. Heck, B. Thybusch
Fachgebiet Chemische Analytik
Fachbereich Material- und Geowissenschaften
Technische Universität Darmstadt (Germany)

Dr. B. T. Poe
Bayerisches Geoinstitut
Universität Bayreuth
95440 Bayreuth (Germany)

Prof. Dr. I-W. Chen
University of Pennsylvania
3231 Walnut Street, 424 LRSM
Philadelphia, PA 19104-6272 (USA)

[+] Current address: Materials Department
University of California, Santa Barbara
Santa Barbara, CA 93436 (USA)
Fax: (+1) 805-893-8486

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formal charge of +4 (4-4 spinels). It was motivated by the observation that β -sialon can be formally derived from β - Si_3N_4 by substituting SiN pairs by AlO. Thus, the composition follows the formula $\text{Si}_{3-x}\text{Al}_x\text{O}_x\text{N}_{4-x}$,^[5] whereby the β - Si_3N_4 structure is known to exist up to $x_{\text{max}} \approx 2.1$. The composition $\text{Al}_3\text{O}_3\text{N}$, corresponding to full substitution ($x=3$), is said to have spinel structure but in fact has not been observed to the present day.^[6] However, at even higher degrees of AlO insertion ($4.2 \leq x \leq 4.7$; $\text{Al}_{[3+(x-3)/3]}\text{O}_x\text{N}_{[1-(x-3)/3]}$), stable spinels containing (cation-vacancy-type) defects, the so called γ -alons, are known.^[7] Their existence and the discovery of the spinel γ - Si_3N_4 ($\equiv c$ - Si_3N_4)^[4a, 8] prompted us to investigate the possible formation of γ -sialon with the composition $\text{Si}_{3-x}\text{Al}_x\text{O}_x\text{N}_{4-x}$ at high pressure.

For our experiments we chose a single-phase β -sialon starting material with $x=1$ (Si_2AlON_3). The composition was verified by X-ray powder diffraction (XRD), by using the known dependence of lattice constants on x ^[9], and electron-probe microanalysis (EPMA). Scanning electron microscopy (SEM) revealed grain sizes of 1–2 μm . High-pressure conversion was carried out in a 6-8 type multi-anvil (MA) apparatus.^[8, 10] The applied pressure of 13 GPa was slightly above that at which γ - Si_3N_4 was synthesized.^[8]

While the color of the starting material was white, the recovered sialon had a dark gray, opaque appearance. SEM studies of fractured surfaces of the starting sialon showed equiaxed grains, similar to kelvin polyhedra, which had changed into more irregular morphologies in the recovered sample. The grain size, however, had decreased to less than 1 μm . A smaller grain size is commonly observed after phase transformations. Within the resolution of SEM, no pores were visible on the ground surface. The chemical composition of the sample, determined by EPMA, was identical to that of the starting sialon and homogeneous within the investigated area (100 $\times$ 100 μm).

The spinel structure was verified by XRD and high-resolution transmission electron microscopy (HR-TEM). Initially, a piece of the recovered sample was ground in an agate mortar. However, we found this caused considerable wear of the mortar (evidenced by surface roughening) because of the high hardness of the material. The resulting XRD pattern (data set I) showed the presence of α -quartz that could be traced to debris from the mortar. A volume fraction of quartz as high as 20% was determined in a Rietveld refinement. Using the quartz as an internal standard, we determined a lattice parameter $a_0^{\text{I}} = 7.823$ Å. In a second approach, a piece of the recovered material was mounted in a capillary on a Gandolfi camera. The diffraction pattern of this sample, with the background subtracted (data set II), is shown in Figure 1, along with its Rietveld difference plot. All reflections can be assigned to a spinel structure. This proves the presence of a single-phase material, hereafter named γ - Si_2AlON_3 .

The geometry of the Gandolfi method causes the lattice constant a_0^{II} to critically depend on the exact value of the distance between the sample and the X-ray film or imaging plate. We therefore consider a_0^{I} derived from data set I using quartz as a standard to be more precise. In contrast, the recorded intensities are not affected, and Rietveld refinement

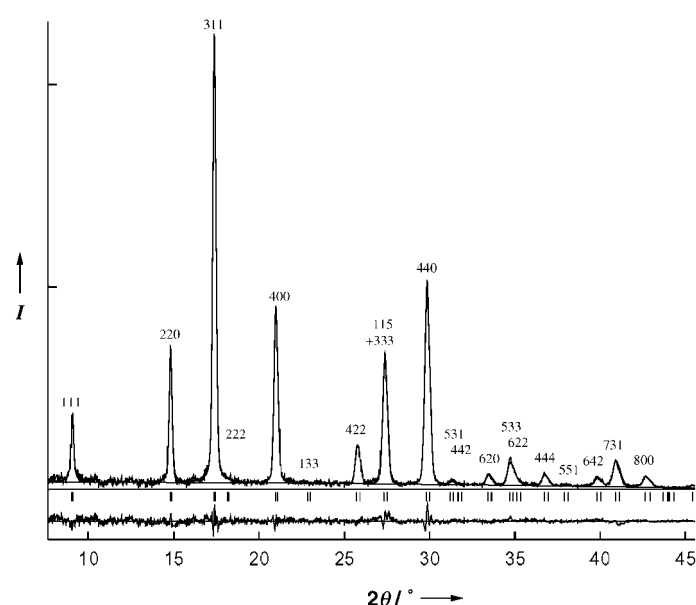


Figure 1. Powder X-ray diffractogram of γ - Si_2AlON_3 (background subtracted) and the corresponding Rietveld difference plot. The line positions are indicated with respect to $\text{MoK}_{\alpha 1}$ and $\text{MoK}_{\alpha 2}$ radiation, respectively.

using data set II yielded better GOF and R_{Bragg} than of data set I. The crystallographic data for both data sets are listed in Table 1. Table 2 lists the atomic coordinates from the respective refinements.

In the spinel structure, the anions are located at (x,x,x) (Wyckoff position 32e), and $x \equiv x_{\text{N/O}}$ is the only free param-

Table 1. Crystallographic data for γ - Si_2AlON_3 .

γ - Si_2AlON_3	data set I	data set II
M_r [g mol ⁻¹]	141.17	
Space group	$Fd\bar{3}m$ (no. 227)	
Radiation, λ [Å]	$\text{CuK}_{\alpha 1}$, 1.54056	MoK_{α} , 0.7107
Lattice param. a_0 [Å]	7.8234(3)	7.7994(7) ^[a]
V [Å ³]	478.76	474.44 ^[a]
Z	8	8
ρ_{calcd} [g cm ⁻³]	3.92	3.95 ^[a]
Profile range	$18.0 \leq 2\theta \leq 87.9^\circ$	$7.6 \leq 2\theta \leq 45.9^\circ$
Step size	$2\theta = 0.02^\circ$	$2\theta = 0.02^\circ$
Varied parameters	37 ^[b]	21
Profile function	pseudo-Voigt	pseudo-Voigt
R values [%]	$R = 4.80$ $R_w = 6.36$ $R_{\text{Bragg}} = 6.99$ GOF: 2.05	$R = 8.54$ $R_w = 13.61$ $R_{\text{Bragg}} = 4.56$ GOF: 1.55

[a] Value of a_0^{II} not corrected for uncertainties in the sample-to-imaging-plate distance. [b] Including parameters for quartz.

Table 2. Atomic coordinates for γ - Si_2AlON_3 .

Data set	Atom	Wyckoff position	x	y	z	B_{iso}
I	Al/Si	8a	1/8	1/8	1/8	1.40(6)
	Si/Al	16d	1/2	1/2	1/2	−1.8(1) ^[b]
	N/O ^[a]	32e	0.2591(2)	0.2591(2)	0.2591(2)	5.2(1) ^[b]
II	Al/Si	8a	1/8	1/8	1/8	1.23(8)
	Si/Al	16d	1/2	1/2	1/2	1.3(1) ^[b]
	N/O ^[a]	32e	0.2550(4)	0.2550(4)	0.2550(4)	2.4(1) ^[b]

[a] For N/O at 32e: $x = y = z = x_{\text{N/O}}$. [b] Isotropic equivalents.

eter. In a spinel with an ideal fcc anion lattice, $x_{\text{N/O}}$ is equal to $1/4$.^[11] A deviation from this value leads to a distorted environment of the octahedral cation sites. The parameter $x_{\text{N/O}}$ is often referred to as “spinel parameter” u and is used to compare anion environments, as shown below.^[12, 13] In the present case a value of $x_{\text{N/O}}^{\text{II}} = 0.255$ ($R_{\text{Bragg}} = 4.56$) was determined from data set II, while data set I yielded $x_{\text{N/O}}^{\text{I}} = 0.259$ ($R_{\text{Bragg}} = 6.99$). From a_0^{I} and $x_{\text{N/O}}^{\text{I}}$, we calculated the average bond lengths between the tetrahedrally and octahedrally coordinated cations and their nearest anionic neighbors, hereafter called $\langle \text{tet-N/O} \rangle$ and $\langle \text{oct-N/O} \rangle$, respectively (Table 2).^[14] The values for $\gamma\text{-Si}_3\text{N}_4$, $\gamma\text{-Si}_2\text{AlON}_3$, and three oxygen-rich γ -alons are listed in Table 3. A comparison between $\gamma\text{-Si}_3\text{N}_4$ and $\gamma\text{-Si}_2\text{AlON}_3$ reveals that $\langle \text{tet-N/O} \rangle$ has decreased from 1.805 to 1.762 Å, while $\langle \text{oct-N/O} \rangle$ has increased from 1.863 to 1.918 Å. The latter change is apparently responsible for the lattice expansion from 7.74 to 7.82 Å. Further insertion of AlO probably causes $\langle \text{tet-N/O} \rangle$ to lengthen, since the (ambient-pressure) γ -alons reported in [12] have $\langle \text{tet-N/O} \rangle$ values of around 1.8 Å. This phenomenon can be explained by assuming preferences of the Si and Al atoms for tetrahedral and octahedral sites, respectively. First, we note that the $\text{Si}_{\text{tet}}\text{-N}$ bond in $\gamma\text{-Si}_3\text{N}_4$ is longer than that in both α - and $\beta\text{-Si}_3\text{N}_4$ to match the larger SiN_6 octahedra in $\gamma\text{-Si}_3\text{N}_4$.^[8, 15] In $\gamma\text{-Si}_2\text{AlON}_3$, on the other hand, some Si_{oct} are now replaced by Al_{oct} , and this would allow the Si-centered tetrahedra to shrink towards their “normal” size. In γ -alons, however, both octahedral and tetrahedral sites are occupied by the bulkier Al ion, and hence the tetrahedral bond length increases again. This explanation is consistent with the observed variations of bond length and the expectations from the consideration of cation size.

The above discussion suggests that $\gamma\text{-Si}_2\text{AlON}_3$ is an inverse spinel in which the lower valent cation preferentially occupies the sites with higher coordination numbers. (The opposite case is referred to as a normal spinel.) This is further supported by a comparison with the structural parameters of known spinels: The anion parameters u of 2-3 and 4-2 spinels (here the numbers refer to the cation valences), when plotted against the ratio of $\langle \text{oct-O} \rangle$ and $\langle \text{tet-O} \rangle$, are known to follow distinct curves on which the data points for inverse and normal spinels are located in separate sections (see p. 3289 in ref. [22]). In the case of our 4-3 spinel, with $u \equiv x_{\text{N/O}} = 0.255$, the calculated data point lies close to the section of inverse spinels. The fraction of site occupation, however, could not be determined from the present XRD data. We also should note that

the preference of Al for the octahedral site may not always be obeyed, as the actual fraction of site occupation of a spinel sialon with fixed composition is likely to depend on pressure, temperature, and the processing history of the material.

We have already noted that the determined lattice constant a_0 of $\gamma\text{-Si}_2\text{AlON}_3$ is 0.085 Å larger than that of $\gamma\text{-Si}_3\text{N}_4$ (Table 3). A linear increase of a_0 with increasing AlO content is well known for $\beta\text{-Si}_{3-x}\text{Al}_x\text{O}_x\text{N}_{4-x}$.^[9] Assuming a similar linear relation between lattice parameter and AlO content for $\gamma\text{-Si}_{3-x}\text{Al}_x\text{O}_x\text{N}_{4-x}$ ($0 \leq x \leq 3$), this correlation would extrapolate to the γ -alons $\text{Al}_{[3+(x-3)/3]}\text{O}_x\text{N}_{[1-(x-3)/3]}$ ($3 \leq x \leq 6$) if $\gamma\text{-Al}_3\text{O}_3\text{N}$ were to exist. Since stoichiometric $\gamma\text{-Al}_3\text{O}_3\text{N}$ has never been reported,^[6] we tried to estimate its lattice constant using data from three independent sources (Figure 2A): i) extrapolation of the two data points $a_0(x=1)$ [$\gamma\text{-Si}_2\text{AlON}_3$] from this work and $a_0(x=0)$ [$\gamma\text{-Si}_3\text{N}_4$] from ref. [8] yielded a value of 7.994 Å for $a_0(x=3)$; ii) extrapolation of the lattice constants of three Al_2O_3 -rich γ -alons investigated by Willems et al. using neutron diffraction^[12] yielded a value of about 7.980 Å; and iii) extrapolation of the lattice parameters of spinels in the Mg–Al–O–N system yielded a value of 7.986 Å.^[16] Thus, the three estimations give very similar results and support the hypothesis of a linear relation for $\gamma\text{-Si}_{3-x}\text{Al}_x\text{O}_x\text{N}_{4-x}$ (Figure 2A).

The compositional location of all nine data points within the reciprocal salt system $\text{SiO}_2\text{–Al}_2\text{O}_3\text{–AlN–Si}_3\text{N}_4$ is shown in Figure 2B. It is clear from Figure 2A that $\gamma\text{-Al}_3\text{O}_3\text{N}$ has a lower atomic density (ca. $9 \text{ Å}^3 \text{ atom}^{-1}$) than $\gamma\text{-Si}_3\text{N}_4$ ($8.27 \text{ Å}^3 \text{ atom}^{-1}$). The density of $\alpha\text{-Al}_2\text{O}_3$ is $8.49 \text{ Å}^3 \text{ atom}^{-1}$, and those of AlN are 8.35 and $8.27 \text{ Å}^3 \text{ atom}^{-1}$ for the low-^[17] and high-pressure^[18] modification, respectively. Only $\gamma\text{-Al}_2\text{O}_3$, with the defect spinel structure ($1/6$ sites empty), has a lower density ($9.3 \text{ Å}^3 \text{ atom}^{-1}$).^[19] Thus, according to Le Chatelier’s principle, on compression, $\gamma\text{-Al}_3\text{O}_3\text{N}$ should always be unstable with respect to decomposition into denser phases. This suggests that sialons of a sufficiently high AlO content cannot be converted to spinels under pressure.

Raman spectra with a spatial resolution of about 20 μm were taken from various parts of the $\gamma\text{-Si}_2\text{AlON}_3$ sample. All spectra were similar to that shown in Figure 3A showing broadened lines at 520, 830, 968, and 1020 cm^{-1} . Such line broadening and elevated background are most probably due to the submicrometer grain size and lattice defects. Similar results were observed for $\gamma\text{-Si}_3\text{N}_4$ synthesized^[8] in a multi-anvil apparatus.^[10a] In comparison, spectrum B in Figure 3 was taken from a $\gamma\text{-Si}_3\text{N}_4$ sample synthesized^[20] in a diamond-anvil cell.^[10a]

Table 3. Lattice parameters and relevant interatomic distances of different compositions in the $\gamma\text{-Si}_3\text{N}_4\text{–Alon–Al}_2\text{O}_3$ system.

	$\gamma\text{-Si}_3\text{N}_4$	$\gamma\text{-Si}_2\text{AlON}_3$	$\text{Al}_{3.35}\text{O}_{4.05}\text{N}_{0.65}$	$\text{Al}_{3.46}\text{O}_{4.38}\text{N}_{0.54}$	$\text{Al}_{3.54}\text{O}_{4.62}\text{N}_{0.46}$
Ref.	[8]	this work	[12]	[12]	[12]
a_0 [Å]	7.7381(2)	7.8234(3) ^[a]	7.9526(5)	7.9435(2)	7.9376(6)
$x_{\text{N/O}}$, $3m$	0.25968(1)	0.2550(4) ^[b]	0.2562(2)	0.2563(1)	0.2552(2)
$x_{\text{N/O}}$, $43m$	0.38468(1)	0.3800(4) ^[b]	0.3812(2)	0.3813(1)	0.3802(2)
$\langle \text{tet-N/O} \rangle$ [Å]	1.805	1.762	1.807	1.807	1.790
$\langle \text{oct-N/O} \rangle$ [Å]	1.863	1.918	1.940	1.937	1.944
$\langle \text{oct-N/O} \rangle / \langle \text{tet-N/O} \rangle$	1.032	1.089	1.073	1.072	1.086
$\langle \text{tet-oct} \rangle$ [Å]	3.208	3.243	3.297	3.293	3.291
$\langle \text{oct-oct} \rangle$ [Å]	2.737	2.766	2.812	2.808	2.806

[a] From data set I. [b] From data set II.

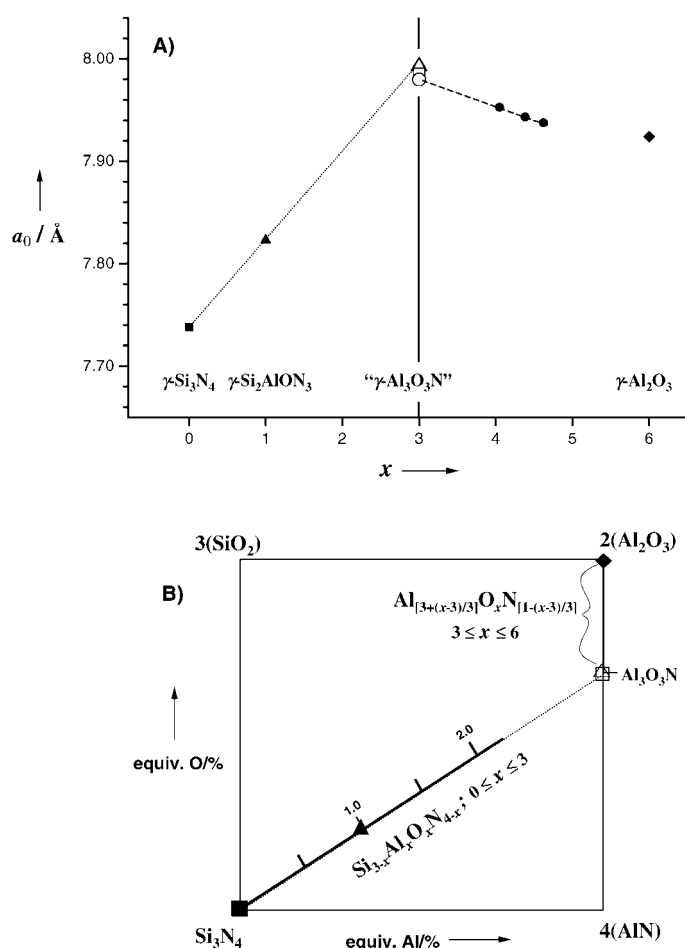


Figure 2. A) Lattice constants of different phases in the $\gamma\text{-Si}_3\text{N}_4\text{-alon-Al}_2\text{O}_3$ system. ■: ref. [8]; ▲: this work; △: extrapolated from ■ and ▲; □: ref. [16]; ●: ref. [12]; ○: extrapolated from ●; ◆: ref. [19]. B) Compositional location of data points in A) within the reciprocal salt system $\text{SiO}_2\text{-Al}_2\text{O}_3\text{-Si}_3\text{N}_4\text{-AlN}$.

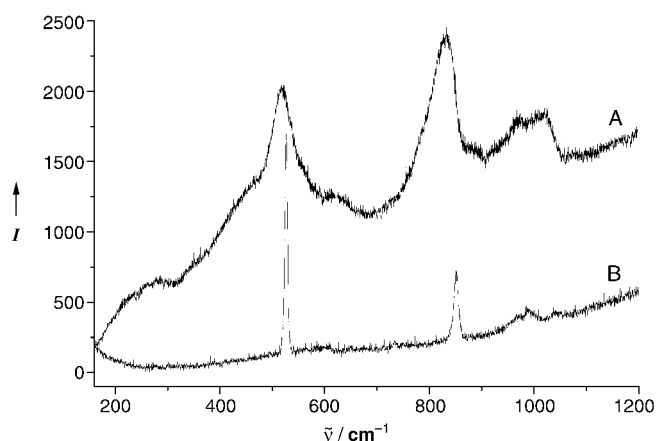


Figure 3. Raman spectra of the spinel nitrides $\gamma\text{-Si}_2\text{AlON}_3$ (A) and $\gamma\text{-Si}_3\text{N}_4$ (B). The spectrum of $\gamma\text{-Si}_2\text{AlON}_3$ (A) was measured at ambient pressure. The spectrum of $\gamma\text{-Si}_3\text{N}_4$ (B) was measured in a diamond-anvil cell at 1.1 GPa.

Here, the sharp bands indicate a well-crystallized material with a small amount of defects. This spectrum was obtained at 1.1 GPa, but the pressure dependence of the spectrum is small as the ambient-pressure frequencies are only 2–4 cm^{-1} lower

than those at 1.1 GPa.^[20] Comparing these Raman bands revealed a slight blue shift in the sialon sample, which may be due to the presence of Al and O ions within the spinel lattice.

Figure 4 shows an SEM image of Vickers indentations on the ground surface of $\gamma\text{-Si}_2\text{AlON}_3$. The quantities $2a$ and $2c$, used for determination of hardness and indentation fracture

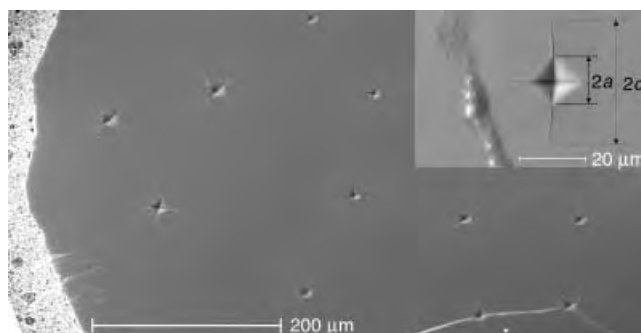


Figure 4. SEM image of $\gamma\text{-Si}_2\text{AlON}_3$ surface with $\text{HV}_{0.5}$ and HV_1 Vickers indentations and their radial crack systems. Inset: A $\text{HV}_{0.5}$ impression with indication of the indentation diagonal $2a$ and crack length $2c$.

toughness, are indicated. The average hardness from ten indentations at 0.5 kg ($\text{HV}_{0.5}$) and four indentations at 1.0 kg (HV_1) is as high as 2800 ± 60 (27.5 GPa). The HV_{10} values for the single-phase α - and β -sialons are usually 2200 and 1800, respectively,^[1, 9] and HV_{10} of γ -alon was also reported to be in the range of 1800.^[7] Therefore, γ -sialon appears to be a harder material. Since hardness is known to decrease with increasing applied load, future experiments on a larger specimen with a higher load (10 kg or more) would be desirable to confirm this observation.

Finally, a fracture toughness of $4.6 \text{ MPa m}^{1/2}$ was determined from the mean indentation crack length ($2c$). This is in the upper range of the toughness values for single-phase, fine-grain α - and β -sialons (typically 3–4.5 $\text{MPa m}^{1/2}$).^[1, 9]

Recently, it was shown that γ -sialons can also be synthesized by shock-compression techniques,^[21] which enable the preparation of larger amounts than the MA technique.^[10a] Also recently, we were able to synthesize γ -sialons with compositions $x = 1.1, 2.0$, and 2.1 . Since spinel oxides encompass many desirable materials with magnetic, magnetoresistant, superconductive and other functional properties of technological relevance,^[22] the extension from spinel oxides to spinel oxide nitrides may hold great promise for the discovery of further novel and useful materials.

Experimental Section

Synthesis of β -sialon starting material: a powder mixture of 66.61 wt % Si_3N_4 (SN-E-10, Ube Industries, Japan, 1.32 wt % O), 11.40 wt % AlN (Type F, Tokuyama Soda Co., CA, 0.9 wt % O), and 21.99 wt % Al_2O_3 (AKP 50, Sumitomo Chemical America, NY) was prepared to give the nominal composition Si_2AlON_3 (the residual oxygen contents of the nitrides were taken into account). The powder was attrition-milled in isopropyl alcohol for 2 h with high-purity Si_3N_4 milling medium in a Teflon-coated jar. The slurry was dried in a polyethylene beaker under a halogen lamp while being stirred. Finally, charges of the powder were uniaxially hot-pressed (30 MPa) in a graphite furnace (1775 °C/2 h/ N_2). Phase analysis was performed by XRD with $\text{CuK}\alpha$ radiation and Si as an internal standard. The analysis showed mostly β -phase with a small amount (< 2%) of $\alpha\text{-Si}_3\text{N}_4$.

The lattice constant of the β -phase was in good agreement with the composition Si_2AlON_3 .^[9]

High-pressure synthesis of γ -sialon was performed in a 6-8 type multi-anvil (MA) apparatus. A detailed description of similar MA devices is given elsewhere.^[10]

A cylinder ($\varnothing = 1.45$; $h = 2.7$ mm; $m = 12.5$ mg) was cored out of a hot-pressed β -sialon compact, wrapped in a 25 μm thick Pt foil, and placed inside a set of coaxially arranged ceramic components (from inside to outside): MgO insulation, LaCrO₃ resistance heater, ZrO₂ tubing. The further pressure assembly was identical that in ref. [8]. The sample was brought to maximum pressure at about 25 °C, heated to 1800 °C at about 100 K min⁻¹, and then immediately quenched to room temperature in less than 15 s. Temperatures were measured with W₇₇Re₃–W₇₅Re₂₅ thermocouples. For details on temperature measurement and pressure calibration see ref. [10b,c].

Surface preparation: The obtained γ -sialon and a piece of the β -sialon phase were embedded in a glass-fiber-filled diallylphthalate matrix (Resin 5, Struers) and wet ground down to 4000 mesh SiC paper to give a surface suitable for indentation measurements. For SEM and EPMA, the sample was sputtered with a ca. 10-nm film of carbon.

HR-SEM was performed on a Philips XL30 FEG with a lateral resolution of 1 nm.

EPMA: Cameca SX-50. Measurements at 20 kV and 20 nA for all elements. Mappings at 20 kV, 49 nA, beam-scan mode, 256 $\times$ 256 data points, step size $\sim$ 0.4 μm . Detectors: TAP for Al, 30 s/data point; PET for Si, 30 s/data point; and PC1 for N and O, 60 s/data point for each element.

X-ray powder diffractometry: Data set I was obtained from the quartz-contaminated γ -sialon, measured in transmission geometry on a Stoe STADI-P diffractometer equipped with a position-sensitive detector covering 6°. The diffractogram of the pure material (data set II, Figure 1) was obtained as follows: A piece of γ -Si₂AlON₃ (70 μm in diameter, ca. 20 μm thick) was split from the central portion of the cylindrical sample. It was mounted on a capillary in a Gandolfi camera. By using a fine-focus rotating anode (GX21, Enraf-Nonius), a two-dimensional diffraction pattern was detected with a flat imaging plate (23 $\times$ 25 cm) positioned at a distance of 119 mm from the sample. It was read out with a spatial resolution of 50 μm with an imaging analyzer (BAS-1800II, Fuji Film). To obtain a standard one-dimensional diffraction pattern (data set II), the intensities were integrated along the azimuthal direction.

Rietveld refinement was carried out with the program LHPM-7^[23] and the scattering curves of neutral atoms were used, since Si⁴⁺, Al³⁺, O²⁻, and N³⁻ scattering curves lead to nearly the same result. Also, no significant difference could be seen on positioning Al at 8a and Si at 16d, or vice versa. The temperature parameters of the 16d and 32e site were treated anisotropically.

Micro-Raman spectroscopy: Ar-ion laser ($\lambda = 457.9$ nm, 2020-05S, Spectra-Physics, San Jose, CA); double spectrometer (SPEX 1402, Spex Industries, Metuchen, NJ) with a charge coupled device detector (LN/CCD-1100 FB, Princeton Instruments, Trenton, NJ, lateral resolution $\sim$ 20 μm).

Vickers hardness measurements were made under ambient atmosphere with a LECO M-400 G2 hardness tester. Each hardness value HV was calculated according to equation (1) where P is the load in kilograms, $\phi = 136^\circ$ the apex angle of the Vickers pyramid, and $(2a)$ the mean indentation diagonal (Figure 4).^[24] A mean HV_{0.5} value of 2789 ± 64 was obtained from ten indentations at a load of 0.5 kg, and four further indentations with a 1-kg load (HV₁) gave 2838 ± 32 ; this led to an overall mean Vickers hardness of 2808 ± 60 (ca. 27.5 GPa). The peak load was applied for 10 s in all cases.

$$\text{HV} = P2 \sin(\phi/2) / (2a)^2 \quad (1)$$

Indentation fracture toughness (K_{IC} -IF) was determined by assuming a Palmquist crack geometry; because of its good correlation to bending-test derived data, the formula given by Shetty was chosen.^[25] A mean K_{IC} -IF of 4.6 MPa m^{1/2} was calculated from four of the 0.5-kg and three of the 1-kg indentations, by using the mean crack lengths $(2c)$ and indentation diagonals $(2a)$ obtained for each indentation and the respective hardness values in SI units. The ratio $\langle c \rangle / \langle a \rangle$ varied between 2.5 and 3.2 for all indentations.

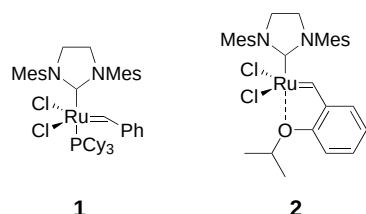
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A Highly Active and Air-Stable Ruthenium Complex for Olefin Metathesis**

Hideaki Wakamatsu and Siegfried Blechert*

Over the past ten years, olefin metathesis has made rapid progress in the field of synthetic organic chemistry.^[1] In 1999 a major step forward has been made with the development of ruthenium alkylidene **1** (Scheme 1).^[2] Studies on the mechanism of olefin metathesis reactions promoted by **1** and its

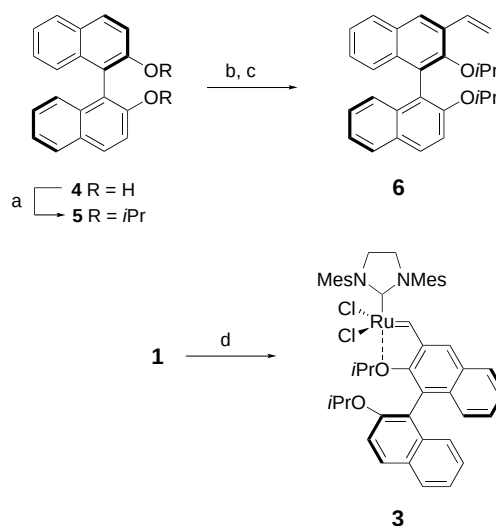


Scheme 1. Ruthenium precatalysts **1** and **2**.

bisphosphane analogue^[3] have revealed that a low ratio of phosphane reassociation to substrate binding was necessary for high activity. Recently, a phosphane-free *N*-heterocyclic carbene complex **2** (Scheme 1) has been described^[4,5] and an immobilized version is also known.^[6] Precatalyst **2** has a superior stability to **1** and is even recoverable by column chromatography. We have found though, that in general this comes hand in hand with longer reaction times. Herein, we report the discovery of a variant of **2** with a similar stability, but with an activity that significantly surpasses that of **1**. The advantages associated with the use of **2** over **1** in cross-metathesis (CM) reactions involving highly electron-deficient olefins are becoming apparent,^[7] especially for CM with challenging substrates such as acrylonitrile and fluorinated olefins.

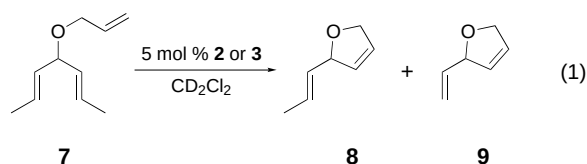
Given this difference in reactivity, a stabilizing interaction between the isopropoxy group and the metal center during metathesis could not be excluded. This presumption prompted us to prepare a chiral chelating isopropoxystyrene ligand for possible asymmetric ring-closing metathesis (ARCM). Only quite recently, the first ruthenium-catalyzed ARCM was described.^[8] We planned to prepare complex **3** (see Scheme 2). The *C*₂-symmetric, chiral 2,2'-dihydroxy-1,1'-binaphthyl (binol) **4** is useful for asymmetric synthesis,^[9] and we expected that **3** would have a similar stability as **2**.

The synthetic route to **3** is shown in Scheme 2. Ligand **6** was readily prepared from commercially available **4** by treatment with *i*PrBr followed by monoformylation and Wittig olefination. Complex **3** could be produced in good yield by reaction of **1** with **6** in the presence of CuCl as a phosphane scavenger in CH₂Cl₂, and isolated by column chromatography.



Scheme 2. Synthesis of **3**. a) 1) NaH, DMF, 2) *i*PrBr, RT, 80%; b) 1) *n*BuLi, THF, 0°C, 2) DMF, RT, 28%, (**5** (49%) recovered); c) Ph₃P⁺CH₃Br⁻, *t*BuOK, Et₂O, 0°C, 96%; d) **6** (2 equiv), CuCl (1 equiv), CH₂Cl₂, 40°C, 76%.

The potential of **3** in ARCM was tested with ether **7** [Eq. (1)]. This reaction was carried out at room temperature in CD₂Cl₂ and monitored by ¹H NMR spectroscopy. In



addition to **8**, vinyl dihydrofuran **9** was also obtained in all cases (**8**:**9**=7:3, determined by GC). We postulate that **9** arises as a result of the reaction between **8** and a methylenecarbenium complex. Disappointingly, no asymmetric induction was observed by GC on a chiral column.

Interestingly, with precatalyst **3**, RCM required only 5 min to reach completion, compared to 30 min using **2**. This enhanced reactivity prompted us to undertake a more systematic study to compare the performance of catalysts **1–3** in RCM reactions. Thereupon, the RCM of **10** to **11** promoted by **1**, **2**, or **3** was controlled by HPLC, and conversions were determined (Figure 1). All reactions were carried out at room temperature in CH₂Cl₂ in the presence of 1 mol % of precatalyst. Surprisingly, the activity of complex **3** was drastically higher than that of not only **2** but also of the phosphane-based catalyst **1**. In general, an increased reactivity in metathesis catalyst is coupled with a decreased stability. To our delight, complex **3** retained all of its activity after being exposed to air for one week.

Subsequently, the performance of **3** compared to that of the benchmark complex **1** was tested in RCM reactions with various substrates (Table 1). The superiority of complex **3** compared to complex **1** over shorter reaction times (turnover frequencies) could be demonstrated in all cases. For example, the reaction of **18** yielded azepin **19** in nearly quantitative

[*] Prof. Dr. S. Blechert, Dr. H. Wakamatsu
Institut für Chemie
Technische Universität Berlin
Strasse des 17. Juni 135, 10623 Berlin (Germany)
Fax: (+49)30-31423619
E-mail: Blechert@chem.tu-berlin.de

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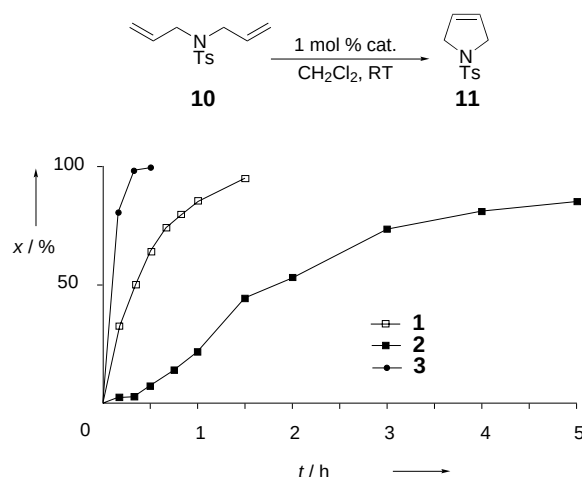


Figure 1. RCM of **10** using catalysts **1**, **2**, or **3**. x = conversion.

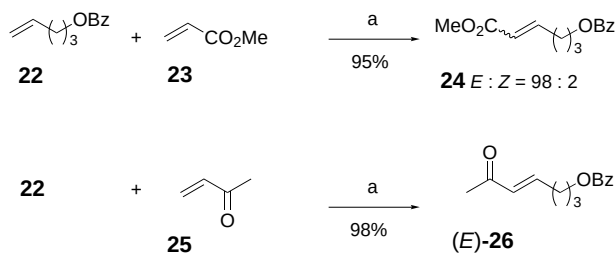
Table 1. Results of RCM using **1** or **3** (1 mol %).^[a]

Entry	Substrate	Product	t [min]	Yield using 3 ^[b] [%]	Yield using 1 ^[c] [%]
1	10	11	30	99	71
2 ^[d]	12	13	30	98	51
3 ^[d]	14	15	90	99	69
4 ^[d]	16	17	20	99	40
5	18	19	10	99	18
6	20	21	20	99	4

[a] All reactions were carried out at room temperature in CH_2Cl_2 (0.01M).

[b] Yield of isolated product after column chromatography. [c] Conversions determined by ^1H NMR spectroscopy. [d] E = CO₂Et.

yield after only 10 min (Table 1, entry 5), whereas under identical conditions, **1** gave only 18% conversion. The greater activity of **3** is especially evident in eight-membered ring formation, which is known to be difficult (Table 1, entry 6). However, the products generated by using **1** were obtained in similar yields if the reaction time was prolonged to a maximum of 4 h. Furthermore, the potential of catalyst **3** for CM reactions was examined (Scheme 3). Catalyst **3** exhibited a high activity in this reaction, even with electron-deficient olefins (**23**, **25**), and the products (**24**, **26**) were obtained in excellent yield after only 20 min.



Scheme 3. CM using **3** (1 mol %). a) CH_2Cl_2 , RT, 20 min.

In summary, the novel binol-based ruthenium alkylidene catalyst **3** exhibits excellent activity and stability in various metathesis reactions. It is clear that the replacement of the isopropoxystyrene ligand in **2** by binol-based styrene **6** results in a large improvement in catalyst activity. We assume that this increase in steric bulk improves the leaving group ability of the ligand, thus facilitating formation of the catalytically active 14-electron species, and suppressing reassociation to the metal center, which supposedly deactivates the catalyst.

Experimental Section

3: CuCl (11 mg, 0.11 mmol) was added to a solution of **6** (83 mg, 0.21 mmol) in dry CH_2Cl_2 (8 mL), then under N_2 **1** (88 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was stirred for 1 h at 40 °C, and then concentrated in vacuo. The residue was dissolved in a minimal volume of CH_2Cl_2 and passed through a Pasteur pipette containing a plug of cotton wool. After concentration in vacuo, the residue was purified by column chromatography on silica gel (hexane/methyl *tert*-butyl ether, 4:1) to afford **3** as a green solid (68 mg, 76 %).^[10]

General procedure for the metathesis reaction using catalyst **3** at room temperature: 1) RCM: Compound **3** (2.0 mg, 2.32 μmol , 1 mol %) was added to a stirred solution of substrate (0.23 mmol, see Table 1) in dry CH_2Cl_2 (23 mL, 0.01M) under N_2 . After TLC analysis showed that the substrate was consumed, the volatiles were removed in vacuo. The residue was purified by column chromatography on silica gel (hexane/methyl *tert*-butyl ether).^[11] 2) CM: Compound **3** (2.0 mg, 2.32 μmol , 1 mol %) was added to a stirred solution of substrate **22** (0.23 mmol) and methyl acrylate (**23**) or methyl vinyl ketone (**25**) (0.46 mmol) in dry CH_2Cl_2 (4.6 mL, 0.05 M) under N_2 . After 20 min the solution was worked up as described under RCM.^[11]

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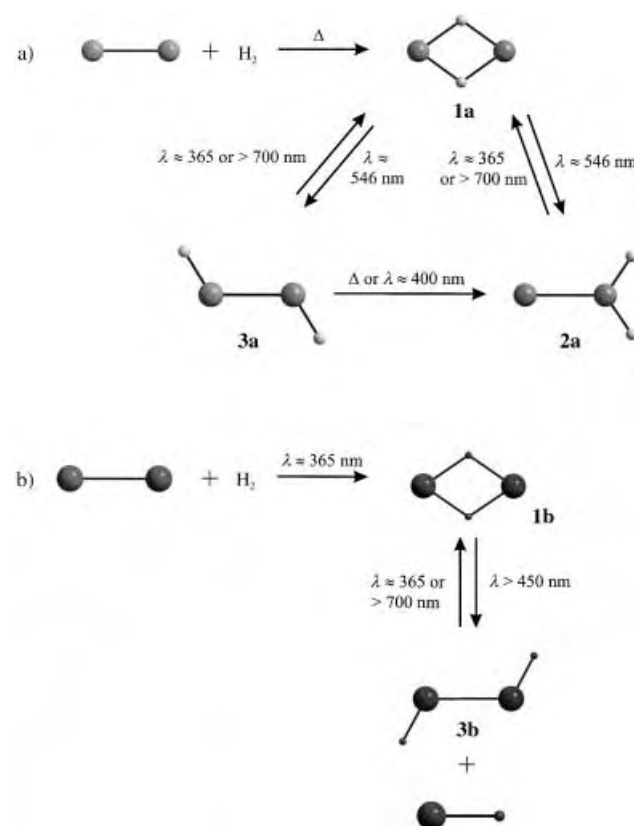
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- [11] ^1H NMR data for the new compounds **21** and (*E*)-**26**; **21**: ^1H NMR (500 MHz, CDCl_3): δ = 1.74 (tt, J = 6, 7 Hz, 2H), 2.22 (dt, J = 6, 7 Hz, 2H), 2.29 (dt, J = 4, 7 Hz, 2H), 2.40 (s, 3H), 3.08 (t, J = 6 Hz, 2H), 3.13–3.15 (m, 2H), 5.66–5.73 (m, 2H), 7.27 (d, J = 8 Hz, 2H), 7.66 (d, J = 8 Hz, 2H); HRMS m/z calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2\text{NS}$ $[\text{M}^+]$: 265.1137, found: 265.1133; (*E*)-**26**: ^1H NMR (500 MHz, CDCl_3): δ = 1.92–1.97 (m, 2H), 2.20 (s, 3H), 2.38 (dt, J = 7, 7 Hz, 2H), 4.34 (t, J = 6 Hz, 2H), 6.11 (d, J = 16 Hz, 1H), 6.81 (dt, J = 16, 7 Hz, 1H), 7.42 (dd, J = 7, 7.5 Hz, 2H), 7.54 (t, J = 7 Hz, 1H), 8.01 (d, J = 7.5 Hz, 2H); HRMS m/z calcd for $\text{C}_7\text{H}_{11}\text{O}_2$ $[\text{M}^+ - \text{COPh}]$: 127.0759, found: 127.0753.

Characterization and Photochemistry of the Gallium and Indium Subhydrides Ga_2H_2 and In_2H_2 **

Hans-Jörg Himmel,* Laurent Manceron,
Anthony J. Downs, and Pluton Pullumbi

Herein we describe the cocondensation of Ga or In vapor with H_2 in an excess of Ar at 10–12 K, and the subsequent irradiation of the resulting matrix with light of different wavelengths. We show that the reaction of Ga_2 or In_2 with H_2

directly or indirectly gives rise to three isomers of Ga_2H_2 and two isomers of In_2H_2 , namely the bis(μ -hydrido) species $\text{Ga}(\mu\text{-H})_2\text{Ga}$ (**1a**) and $\text{In}(\mu\text{-H})_2\text{In}$ (**1b**), the *trans*-bent species HGaGaH (**3a**) and HInInH (**3b**), and GaGaH_2 (**2a**) with two terminal Ga–H bonds (Scheme 1). All these molecules have



Scheme 1. Thermally and photolytically activated reactions taking place in argon matrices a) between Ga_2 and H_2 , and b) between In_2 and H_2 .

been identified and characterized by IR spectroscopy, and by a comparison of the measured spectra with those calculated by quantum-chemical methods as well as with spectra of known gallium and indium hydrides. The findings show that the isomers can be interconverted by selective photolysis.

The Group 13 subhydrides are of interest not only because of the possibility of metal–metal bonding in $\text{M}(\mu\text{-H})_2\text{M}$ species and even of multiple bonding in HMMH species ($\text{M} = \text{Ga}$ or In), but also because of the potential role of gallium and indium hydrides as precursors or intermediates in chemical vapor deposition (CVD) processes designed to produce metallic or semiconductor materials. Although such compounds have attracted considerable attention from theorists, [1–4] experimental information is available only for linear HBBH [5] and for $\text{Al}(\mu\text{-H})_2\text{Al}$ [6] both identified in matrix experiments. Similar experiments with thermally evaporated gallium have suggested [7] that Ga_2 reacts spontaneously with H_2 to form **1a** which, like $\text{Al}(\mu\text{-H})_2\text{Al}$ has the planar structure motif **A**. Of other possible M_2H_2 isomers (structure motifs **B**–**D**), only $\text{HAl}(\mu\text{-H})\text{Al}$ (with structure motif **D**) has been identified, albeit somewhat tentatively. [6]

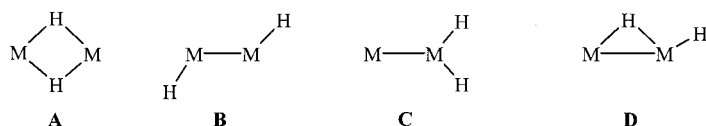
[*] Dr. Dr. H.-J. Himmel
Institut für Anorganische Chemie
Universität Karlsruhe (TH)
Engesserstrasse, 76128 Karlsruhe (Germany)
Fax: (+49) 721-608-4854
E-mail: himmel@chemie.uni-karlsruhe.de

Prof. A. J. Downs
Inorganic Chemistry Laboratory
University of Oxford
South Parks Road, Oxford OX1 3QR (UK)

Dr. L. Manceron
LADIR/Spectrochimie Moléculaire, CNRS UMR 7075 Université
Pierre et Marie Curie
4 Place Jussieu, 75252, Paris Cedex 05 (France)

Dr. P. Pullumbi
Air Liquide, Centre de Recherche Claude-Delorme
BP 126, Les Loges-en-Josas (France)

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Upon deposition of gallium in a solid H₂-doped Ar matrix, five bands appeared in the IR spectrum of the matrix at 2200, 1176, 1002, 906.5, and 880 cm⁻¹, with the band at 1002 cm⁻¹ being an order of magnitude more intense than the other bands (Figure 1). Experiments with different concentrations

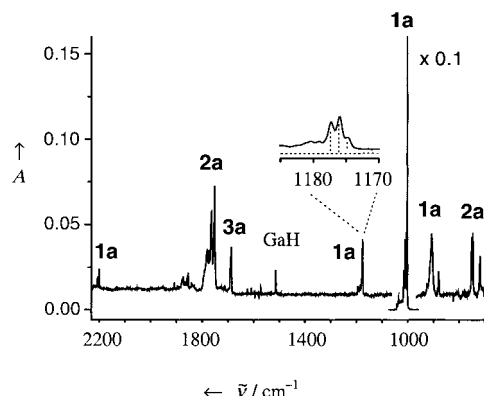


Figure 1. IR spectrum for an Ar matrix containing Ga vapor codeposited with H₂: (Ga/H₂/Ar = 0.6/1/100 deposited at 14 K for 90 min).

of metal or H₂ indicated that these signals all belong to the same absorber **1a**. The relative intensities (2.3:3:1) of the triplet at 1176 cm⁻¹ tally almost exactly with those expected for naturally occurring ⁶⁹Ga and ⁷¹Ga atoms with the freedom to occupy two chemically equivalent sites. Subsequent exposure of the matrix to light of the wavelength $\lambda \approx 546$ nm resulted in the extinction of the signals of **1a** and to the appearance of two sets of bands, attributable to **2a** and **3a**. Compound **2a** is marked by IR bands at 1765, 1752, and 752 cm⁻¹, compound **3a** by just one sharp band near 1686 cm⁻¹ (Figure 2, top). Compound **2a** can be converted into **3a** by

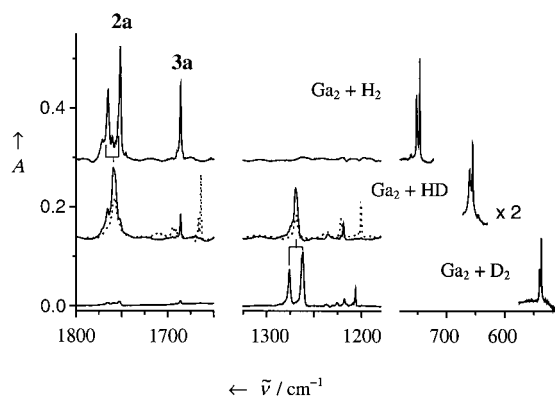


Figure 2. IR difference spectra that were obtained by subtracting the spectra recorded after irradiation at $\lambda = 600$ –800 nm from those recorded after irradiation at $\lambda \approx 546$ nm for samples containing Ga vapor codeposited with 1 % H₂ or HD in an excess of argon. For the HD experiment, the dotted line corresponds to a spectrum recorded 1 min after excitation with green light, the solid line to a spectrum taken 120 min later, after complete evolution.

heating the matrix at temperatures up to 30 K or by irradiation at $\lambda \approx 400$ nm. Photolysis at $\lambda \approx 365$ or > 700 nm leads then to the conversion of **2a** and **3a** back to **1a**.

The experiments were repeated with D₂, HD, and 1:1 mixtures of H₂ and D₂ in place of H₂. In the experiments with D₂, only very weak IR signals attributable to the deuterium derivative of **1a** were visible immediately upon deposition. It required several hours or photolysis with IR light before the signals developed the expected level of intensity. The bands were then located near 1592, 906, 728, 653.6, and 638.4 cm⁻¹. The effects of photolysis were similar to those described for the reaction with H₂. The bands of the deuterium derivatives of **2a** and **3a** are both shifted to lower wavenumbers (**2a**: 1275.8, 1260.1, 540.3 cm⁻¹; **3a**: 1206.4 cm⁻¹; Figure 2 bottom). In the experiments with HD, signals at 2040, 1128/1112, 953, 849, and 676 cm⁻¹ were attributable to the **1a** analogue. The HD analogue of **2a** produced by photolysis displayed absorptions at 1758, 1270, and 665.4 cm⁻¹ (Figure 2, middle). The HD analogue of **3a** was also formed presumably, although at concentrations too low for it to be detected. Finally, the experiment with a 1:1 H₂/D₂ mixture gave spectra which were merely superpositions of those observed in the experiments with H₂ and D₂ recorded separately.

In corresponding reactions with In₂ instead of Ga₂ the formation of a reaction product was initially not observed. A reaction could be induced, however, by irradiation of the matrix at $\lambda \approx 365$ nm. This led to the appearance of five new signals at 2020.8, 1079.1, 954.8, 848, and 800.0 cm⁻¹, of which that at 954.8 cm⁻¹ was the most intense (Figure 3). On the basis of the analogies with the spectrum of **1a**, we identify the compound formed as **1b**. The intensity of signals of **1b** dropped significantly on irradiation of the matrix at $\lambda \approx 365$ nm; simultaneously two new signals appeared at 1518 and 1387.4 cm⁻¹. The signal at 1518 cm⁻¹ can be assigned to a new indium hydride species **3b**, the signal at 1387.4 cm⁻¹ to the known diatomic molecule InH.^[8] Photolysis at $\lambda > 450$ nm led to a rapid decrease of the signal of **3b** and the reappearance of the signals of **1b**.

Experiments with D₂, HD, and 1:1 mixtures of H₂ and D₂ follow the same pattern as those with gallium; the IR transitions of **1b** and **3b** are shifted to lower wavenumbers (D₂ experiments: **1b**: 815.1, 693.1, 611.9, 582.3 cm⁻¹; **3b**: 1081 cm⁻¹; HD experiments: **1b**: 899.6, 630.1, 605.4 cm⁻¹; the HD analogue to **3b** could not be detected).

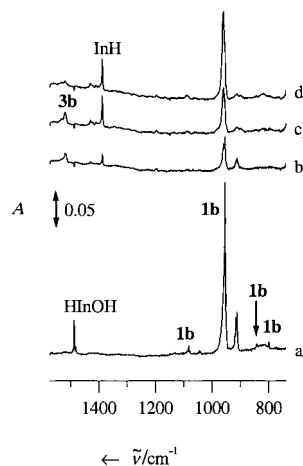


Figure 3. IR spectra recorded for an Ar matrix containing In vapor and 5 % H₂: a) after photolysis at $\lambda \approx 365$ nm; b) after photolysis at $\lambda > 450$ nm; c) after broad-band UV/Vis photolysis at $200 \leq \lambda \leq 800$ nm; and d) after a second cycle of photolysis at $\lambda \approx 365$ nm. HInOH, which exists as an impurity, forms by reaction with traces of H₂O.

The IR spectra show that **1a**, and presumably also **1b**, contain two equivalent metal atoms. On these grounds alone, models **C** and **D** would appear to be excluded. Arguing against model **B**, moreover, is the lack of any stretching modes for terminal Ga–H or In–H bonds (1400–2050 cm^{−1}).^[2] The most plausible interpretation of the results is that **1a** and **1b** are indeed the dihydrido-bridged molecules Ga(μ -H)₂Ga and In(μ -H)₂In with the structure **A**. For a planar molecule of this sort with *D*_{2h} symmetry only three vibrational fundamentals are expected to be IR-active. Calculations in the optimized geometry reveal that one of these modes, corresponding to the ring-puckering mode ν_6 (b_{3u}), will occur at a wavenumber (ca. 200 cm^{−1}) and with an intensity (ca. 1 % that of the strongest absorption) which will make it hard to locate in practice. The intense bands at 1002 (**1a**) and 954.8 (**1b**) cm^{−1} are assigned to the ν_4 (b_{1u}) mode and the weaker bands at 906.5 (**1a**) and 800.0 (**1b**) cm^{−1} to the ν_4 (b_{2u}) mode. The weak bands at 880 (**1a**) and 848 (**1b**) cm^{−1} can then be ascribed to the ν_m (b_{3g}) mode, which is made active by the reduced symmetry (*C*_{2v}) of the ⁶⁹Ga-⁷¹GaH₂/⁷¹Ga⁶⁹GaH₂ and ¹¹³In¹¹⁵InH₂/¹¹⁵In¹¹³InH₂ isotopomers, which each make up a fraction of the product. With the aid of the vibrational modes calculated for the optimized structures, the remaining bands can be attributed to combination modes each of which involves an IR-silent (a_g) fundamental. The net result is that all but one (b_{3u}) of the six fundamentals of the two molecules (2a_g + b_{3g} + b_{1u} + b_{2u} + b_{3u}) have been detected. The assignments are supported by isotope exchange effects (⁶⁹Ga/⁷¹Ga and D for H).

Since the experiments with mixtures of H₂ and D₂ gave no hint of the formation of isotopomers Ga(μ -H)(μ -D)Ga or In(μ -H)(μ -D)In, which would be obtained by using HD, there can be little doubt about the concerted bimolecular nature of the reaction occurring between Ga₂ or In₂ and H₂. Intriguingly, though, the reaction with Ga₂, but not that with In₂, is spontaneous and shows a marked kinetic isotope effect. The reaction is much slower with D₂ than with H₂ or HD at 10–12 K, although it can be accelerated by exposure of the matrix to additional IR radiation.

Tables 1 and 2 compare the wavenumbers observed in the experiments with those calculated by using density functional theory (DFT) methods. The contrasting reactivities of Ga₂

Table 2. Structures and IR properties for the indium hydride species In(μ -H)₂In (**1b**) and HInInH (**3b**).^[a]

	1b		3b	
symmetry	<i>D</i> _{2h}		<i>C</i> _{2h}	
In...In	3.4082		3.0596	
In–H	2.0741		1.8136	
In–H–In	110.5			
H–In–In			120.2	
vibrations	obs.	calcd	obs.	calcd
ν_1	1066.0 ^[b]	1134.2 (0, a _g)	[e]	1505.5 (0, a _g)
ν_2	124.3 ^[b]	140.8 (0, a _g)	[e]	406.2 (0, a _g)
ν_3	848 ^[d]	884.6 (0, b _{3g})	[e]	93.1 (0, a _g)
ν_4	954.8	1048.5 (2268, b _{1u})	[e]	168.0 (18, a _u)
ν_5	800.0	808.1 (244, b _{2u})	1518	1517.9 (1230, b _u)
ν_6	[f]	332.9 (6, b _{3u})	[e]	152.2 (36, b _u)

[a] Calculations at the B3PW91 level of theory; distances in Å, bond angles in °, wavenumbers in cm^{−1}; calculated IR intensities in km mol^{−1} and symmetry assignments in parentheses. [b] Estimated value from a combination band (±5 cm^{−1}). [c] IR-silent. [d] See text. [e] Out of the range of detection in our experiments. [f] Too weak to be detected.

and In₂ pose a teasing problem to which there is no immediate solution. Possible explanations along with full details of all the results, will be reported elsewhere.^[9]

Comparison with the spectra of other gallium and indium hydrides and with the spectra simulated for different Ga₂H₂ and In₂H₂ isomers with the geometries **B–D**, allied with the response to deuteration, leads us to infer that **2a** is GaGaH₂ (**C**), and that **3a** and **3b** are HGaGaH and HInInH, respectively (**B**). The isomerization can be reversed by UV photolysis (λ = ca. 365 nm) of HMMH (M = Ga or In) and GaGaH₂, or by near-IR photolysis (λ > 700 nm) of HGaGaH and GaGaH₂. However, there has been found as yet no trace of isomers of the type HM(μ -H)M (**D**). Scheme 1 summarizes the thermally or photolytically activated reactions described.

Experimental Section

Gallium (Aldrich, purity 99.9999 %) and indium (Aldrich, purity 99.999 %) were each evaporated in either a tantalum or graphite cell or a tungsten filament that was heated resistively to about 900 °C. Further details of the relevant matrix assemblies are given in references [8, 10–12]. The estimated proportions were about 0.5:0.5:100 (M/H₂/Ar, M/D₂/Ar, M/

Table 1. Structures and IR modes of the gallium hydrides Ga(μ -H)₂Ga (**1a**), GaGaH₂ (**2a**), and HGaGaH (**3a**).^[a]

	1a		2a		3a	
symmetry	<i>D</i> _{2h}		<i>C</i> _{2v}		<i>C</i> _{2h}	
Ga...Ga	3.0425		2.7091		2.5848	
Ga–H	1.8767		1.6001		1.6261	
Ga–H–Ga	108.3					
H–Ga–H			109.9			
H–Ga–Ga					121.3	
vibrations	obs.	calcd	obs.	calcd	obs.	calcd
ν_1	1220 ^[b]	1231.6 (0, a _g)	1752.1 ^[b]	1835.8 (509, a ₁)	[e]	1708.9 (0, a _g)
ν_2	175 ^[b]	190.1 (0, a _g)	752	770.0 (367, a ₁)	[e]	502.8 (0, a _g)
ν_3	880 ^[d]	920.0 (0, b _{3g})	[e]	179.3 (13, a ₁)	[e]	163.3 (0, a _g)
ν_4	1002	1032.2 (1946, b _{1u})	[f]	359.2 (73, b ₁)	[e]	223.6 (24, a _u)
ν_5	906.5	865.6 (213, b _{2u})	1765.1	1847.7 (370, b ₂)	1686.1	1727.7 (1046, b _u)
ν_6	[e]	200.7 (18, b _{3u})	[e]	224.4 (23, b ₂)	[e]	186.2 (53, b _u)

[a] Calculations at the B3PW91 level of theory; distances in Å, bond angles in °, wavenumbers in cm^{−1}; calculated IR intensities in km mol^{−1} and symmetry assignments in parentheses. [b] Estimated value from a combination band (±5 cm^{−1}). [c] IR-silent. [d] See text. [e] Out of the range of detection in our experiments. [f] Too weak to be detected.

HD/Ar) and 0.5:1:100 (M/H₂ + D₂/Ar). The deposition rates were about 2 mmol of matrix gas per hour.

Reagents used: H₂ (Air Liquide, 99.995%), D₂ (Isotec, 99.5%), Ar (Messer, purity 4.8). HD was prepared by reaction of LiAlH₄ with D₂O and passed through a liquid N₂ trap (ca. 90% HD and 10% H₂).

Photolysis: high-pressure Xe/Hg arc or a medium-pressure Hg lamp (Philips LP 125, 200 or 125 W, respectively); heating effects of the matrix by IR radiation were minimized by a water filter. Light of the desired wavelengths was delivered by appropriate interference or Pyrex filters.

IR spectra of the matrix samples were recorded mostly in the reflection mode at resolutions ranging from 0.5 to 0.05 cm⁻¹ and with a wavenumber accuracy of ±0.1 cm⁻¹. FTIR spectrometers: Nicolet Magna-IR 560 (in Oxford), Bruker 113v (in Karlsruhe), and Bruker 120 (in Paris).

DFT calculations were performed with the GAUSSIAN 98 program package.^[13] The results reported here are those delivered by the B3PW91 method, with a 6-311G(d) basis set for Ga and a LANL2DZ basis set with additional d-polarization functions (exponent 0.5) for In.

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Carbonyltris(trifluoromethyl)borane, (CF₃)₃BCO, An Unusual Boron Carbonyl**

Annegret Terheiden, Eduard Bernhardt, Helge Willner,* and Friedhelm Aubke*

Dedicated to Professor Hans Bürger on the occasion of his 65th birthday

Since the discovery of carbonylborane, H₃B(CO), by Burg and Schlesinger^[1] in 1937, approximately twenty further boron carbonyl derivatives have been reported and for the most part extensively characterized.^[2,3] These boron carbonyls are isolable under ambient conditions, and were synthesized primarily by the addition of CO to suitable boranes and subhalogenides of boron.^[2] We report here a new mononuclear boron carbonyl compound that was synthesized in an unusual manner: carbonyltris(trifluoromethyl)borane, (CF₃)₃B(CO) (**1**).

The unexpected formation of **1** was observed during attempts to explore the limits of stability of salts of the new tetrakis(trifluoromethyl)borate ion [B(CF₃)₄]⁻.^[4] K[B(CF₃)₄] slowly decomposes at room temperature in concentrated sulfuric acid (96%) to give a volatile product. The gas-phase IR spectrum of this product is shown in Figure 1. A preliminary identification of this material as (CF₃)₃B(CO) is

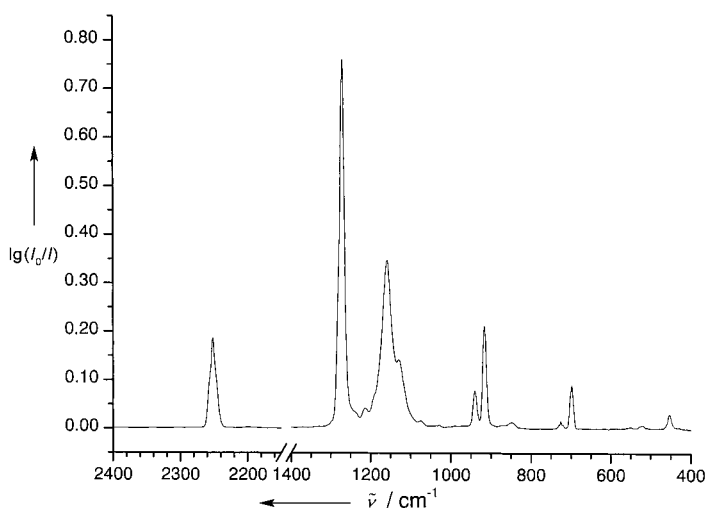


Figure 1. The gas-phase IR spectrum of **1** (0.59 mbar) at 28°C (optical path length 19.5 cm).

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[*] Prof. Dr. H. Willner, Dipl.-Chem. A. Terheiden, Dr. E. Bernhardt
Anorganische Chemie
Gerhard-Mercator-Universität Duisburg
Lotharstrasse 1, 47048 Duisburg (Germany)
Fax: (+49)203-379-2231
E-mail: willner@uni-duisburg.de

Prof. Dr. F. Aubke
Department of Chemistry
The University of British Columbia
Vancouver BC V6T1Z1 (Canada)
Fax: (+1)604-822 2847
E-mail: aubke@chem.ubc.ca

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Table 1. NMR data of **1** and related compounds.^[a]

Compound	$\delta(^{11}\text{B})$	$\delta(^{13}\text{C})$ (CF_3)	$\delta(^{13}\text{C})$	$\delta(^{19}\text{F})$	$^1J(^{11}\text{B},^{13}\text{C})$ (CF_3)	$^1J(^{11}\text{B},^{13}\text{C})$	$^1J(^{13}\text{C},^{19}\text{F})$	$^2J(^{11}\text{B},^{19}\text{F})$	$^3J(^{13}\text{C},^{19}\text{F})$ (CF_3)	$^3J(^{13}\text{C},^{19}\text{F})$	$^4J(^{19}\text{F},^{19}\text{F})$	Ref.
$[(\text{CF}_3)_3\text{BC}(\text{O})\text{OD}]^-$ ^[b]	−19.0	135.0	192.5	−60.6	72.8	67.0	305.1	25.8	4.0	3.4	6.3	[c]
$[\text{B}(\text{CF}_3)_4]^-$	−18.9	132.9	—	−61.6	73.4	—	304.3	25.9	3.9	—	5.8	[4]
1 , CD_2Cl_2 ^[e]	−17.9	126.2	159.8	−58.7	80 ± 5	30 ± 5	298 ± 3	36 ± 2	n.o. ^[e]	n.o. ^[e]	n.o. ^[e]	[d]
1 , SO_2 ^[b]	−17.8	126.7	158.9	−58.3	75 ± 10	30 ± 10	298 ± 3	32 ± 2	n.o. ^[e]	n.o. ^[e]	n.o. ^[e]	[d]
$[(\text{CF}_3)_3\text{B}(\text{OH})]^-$	−10.6	134.7	—	−68.0	75.8	—	311.4	26.8	2.7	—	n.o. ^[e]	[7]

[a] Coupling constants J in Hz. [b] Linewidth 1–2 Hz. [c] Linewidth 30–60 Hz. [d] This work. [e] n.o. = not observed.

based on the observation of a band at 2252 cm^{-1} (characteristic of ν_{CO} in σ -bonded carbonyls),^[5] a band pattern in the range of $1300\text{--}400\text{ cm}^{-1}$ (characteristic of a $\text{B}(\text{CF}_3)_x$ group),^[4, 6] and the absence of vibrational-rotational fine structure (indicative for high moments of inertia due to a large molecular mass). A comparison of the ^{19}F , ^{11}B , and ^{13}C NMR spectra with those of related species (Table 1) provides additional evidence. However the NMR spectroscopic evidence is not unambiguous, since all NMR signals, independent of solvents (CD_2Cl_2 , SO_2) and temperature (-40 to 0°C) are broadened up to 40 Hz so that coupling patterns are not clearly recognizable.

In the EI mass spectrum (70 eV), the ion of highest mass occurs at m/z 227, which is consistent with the ion $(\text{CF}_3)_2^{11}\text{B}(\text{CF}_2)\text{CO}^+$. From vapour density measurements a molecular mass of $246 \pm 2\text{ g mol}^{-1}$ is obtained which agrees well with the calculated value of 245.85 g mol^{-1} . The reaction with CH_3CN at room temperature produces in addition to CO a product, whose Raman spectrum is identical with that of $(\text{CF}_3)_3\text{B}(\text{NCCH}_3)$.^[7]

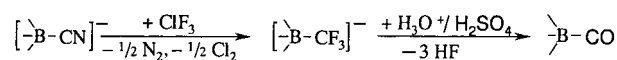
Selected characteristic data for **1**, the CO adduct $\text{F}_3\text{B} \cdot \text{CO}$, $\text{H}_3\text{B}(\text{CO})$, and other typical, thermally stable boron carbonyls are summarized in Table 2. The characteristic feature of all boron carbonyls is the higher wavenumber of the CO stretch than that of free CO (2143 cm^{-1}). This is due mainly to the bond polarization of the CO ligand at the boron atom,^[18] which is also found for thermally stable metal carbonyl cations and their derivatives,^[5, 19] in which CO is σ -bonded to metal cations. Among the boron carbonyls, **1** has the highest wavenumber so far for the CO stretch (2252 cm^{-1}).

In sharp contrast to the synthesis of all other boron carbonyls, where CO is added to suitable starting materials,^[2] in the synthesis of **1** the CO group is generated in situ by the hydrolysis of a single CF_3 group. The reaction step described is thus part of a series of transformations, in which starting from $[\text{B}(\text{CN})_4]^-$,^[20] the B–C bond remains intact, while the nature of the ligand is altered (Scheme 1).

Table 2. Characteristic data of selected carbonyl derivatives.

Compound	ν_{CO} [cm^{-1}]	$r(\text{B}–\text{C})$ [Å]	$D(\text{B}–\text{C})$ [kJ mol^{-1}]	T_{decomp} [$^\circ\text{C}$] ^[a]
$\text{F}_3\text{B} \cdot \text{CO}$	2151 ^[8]	2.89 ^[9]	7.6 ^[17]	−200 ^[2]
$\text{H}_3\text{B}(\text{CO})$	2165 ^[11]	1.54, ^[12] (1.51) ^[10]	141 ^[12]	20 ^[2]
1	2252 ^[b]	(1.58) ^[b]	(112) ^[b]	0 ^[b]
$1,10\text{-B}_{10}\text{H}_8(\text{CO})_2$	2147 ^[13]			200 ^[13]
$1,12\text{-B}_{12}\text{H}_{10}(\text{CO})_2$	2210 ^[13]	1.54 ^[14]		400 ^[13]
$(\text{BF}_3)_3\text{B}(\text{CO})$	2162 ^[15]	1.52 ^[16]		20 ^[16]
$(\text{BCl}_2)_3\text{B}(\text{CO})$	2176 ^[16]	1.54 ^[16]		20 ^[16]

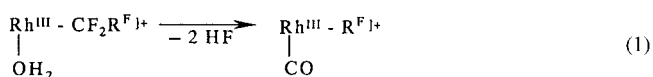
[a] Estimated by behavior described in literature. [b] This work; in parentheses: calculated data.



Scheme 1.

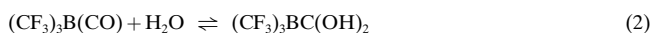
In a vacuum, **1** evolves from the suspension as a gas, which is isolated in a cold trap at -110°C as a colorless, partly crystalline solid in about 95% yield by fractional condensation, using a series of traps held at -30 , -110 , and -196°C . Even though the C–F bond dissociation energy of 485 kJ mol^{-1} is the highest of all carbon–element single bonds, the hydrolysis reaction, which results in the formation of a strong C–O bond, is expected to be exothermic on account of the formation of 3 moles of HF ($3 \times 567\text{ kJ mol}^{-1}$).

There are very few reported precedents for the hydrolysis of a CF_3 group in an acidic environment. In a mechanistic study by Hughes et al.^[21] of a cationic Rh^{III} complex, the $\alpha\text{-CF}_2$ group of a perfluorobenzyl or C_6F_5 ligand was hydrolyzed by coordinated H_2O to a CO group with evolution of HF; in this reaction the C_6F_5 or C_2F_5 ligands, respectively, remain coordinated to the Rh center [Eq. (1), $\text{R}^{\text{F}} = \text{C}_6\text{F}_5$, C_2F_5]. Also in arenes CF_3 substituents are converted in concentrated H_2SO_4 under more severe conditions ($>100^\circ\text{C}$, $>6\text{ h}$) to carboxy groups.^[22]



Compound **1** is a clear, colorless liquid at room temperature with a melting point of $9 \pm 1^\circ\text{C}$. At this temperature the vapor pressure is 38 mbar; the sublimation vapor pressure curve is given by the expression $\ln p = -6162/T + 25.5$ (p in mbar, T in K). Above its melting point, **1** decomposes so quickly that a reliable vapor pressure curve cannot be obtained. In the gas phase, the thermal decomposition appears to be first order with $t_{1/2} = 50\text{ min}$ at 28°C . CO and BF_3 are observed among the decomposition products. In the presence of an excess of ^{13}CO or C^{18}O , the CO ligand in **1** is exchanged, which can be monitored by the increase in intensity of the IR bands at 2200 or 2201 cm^{-1} , respectively. As the observed band positions for the ^{13}C and ^{18}O isotopomers agree well with bands at 2202 and 2198 cm^{-1} , calculated according to the two-mass model, appreciable vibrational mixing for the CO group in **1** is ruled out.

As reported previously for $1,12\text{-B}_{12}\text{H}_{10}(\text{CO})_2$,^[14] **1** is not degraded hydrolytically with water. Instead reversible equilibria (2) and (3) are suggested.



The acidic aqueous solution is stable for several weeks at room temperature. The observed chemical shifts and spin coupling patterns (see Table 1) strongly suggest the presence of a $(\text{CF}_3)_3\text{BC}$ fragment. The exact nature of these species and their concentrations in equilibria (2) and (3) will be the subject of a subsequent investigation. As reported for metal carbonyl cations,^[5, 19] the carbonyl carbon atom in **1** is the electrophilic center. However, unlike in **1** traces of water induce irreversible hydrolysis in metal carbonyl cations.

To support the interpretation of **1**, we carried out calculations using the Gaussian 98 program package^[23] B3LYP/6-31G*. According to these calculations, an equilibrium structure with C_3 symmetry is expected, in which the CF_3 groups are rotated by 13° relative to each other and the B–CO bond length is about 1.58 Å. A rather high value of 3.27 D is predicted for the dipole moment; hence the broad linewidth of the NMR signals is explained by the interaction with the quadrupolar nuclei ^{10}B and ^{11}B . The recorded IR spectrum of **1** agrees well with the calculated one. Using the same basis set to calculate the energies of CO and $\text{B}(\text{CF}_3)_3$, we obtain a bond dissociation energy of 112 kJ mol^{-1} for **1**, which is consistent with the observed low thermal stability of **1**. Finally, calculated partial atomic charges of $q_{\text{B}} = -0.002$, $q_{\text{C}} = +0.404$, and $q_{\text{O}} = -0.166 \text{ e}^-$ are obtained for the B–C–O group, which support our claim that the C(O) atom is the electrophilic center in **1**.

Since the free Lewis acid $\text{B}(\text{CF}_3)_3$ is not stable, a dissociation equilibrium between the primary dissociation products is not observed. The calculated F^- ion affinity for the hypothetical $\text{B}(\text{CF}_3)_3$ molecule is similar to the so far strongest Lewis acids SbF_5 (502 kJ mol^{-1})^[24] and AuF_5 (591 kJ mol^{-1}).^[25]

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Unexpected Carbonyl Mobility in Aminoketoses: The Key to Major Maillard Crosslinks**

Klaus M. Biemel, Jürgen Conrad, and Markus O. Lederer*

Covalently crosslinked proteins are among the major modifications caused by Maillard processes (reactions of reducing sugars with amines) and belong to the so-called 'advanced glycation end products' (AGEs). Most AGEs are formed from aminoketoses **1** via highly reactive dicarbonyl intermediates such as **2–4** (Scheme 1).^[1–3] In long-lived connective tissue and matrix components, AGEs accumulate with age and are generated to a greater extent in diabetes.^[4] AGEs can activate cellular receptors^[5] and contribute to pathophysiology associated with ageing in general as well as

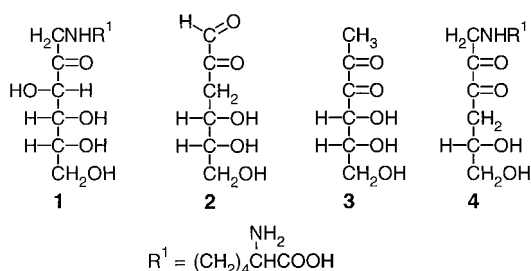
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[*] Priv.-Doz. Dr. M. O. Lederer, K. M. Biemel
Institut für Lebensmittelchemie (170), Universität Hohenheim
Garbenstrasse 28, 70593 Stuttgart (Germany)
Fax: (+49) 711-459-4096
E-mail: ledererm@uni-hohenheim.de
Dr. J. Conrad
Institut für Chemie (130)
Garbenstrasse 30, 70593 Stuttgart (Germany)

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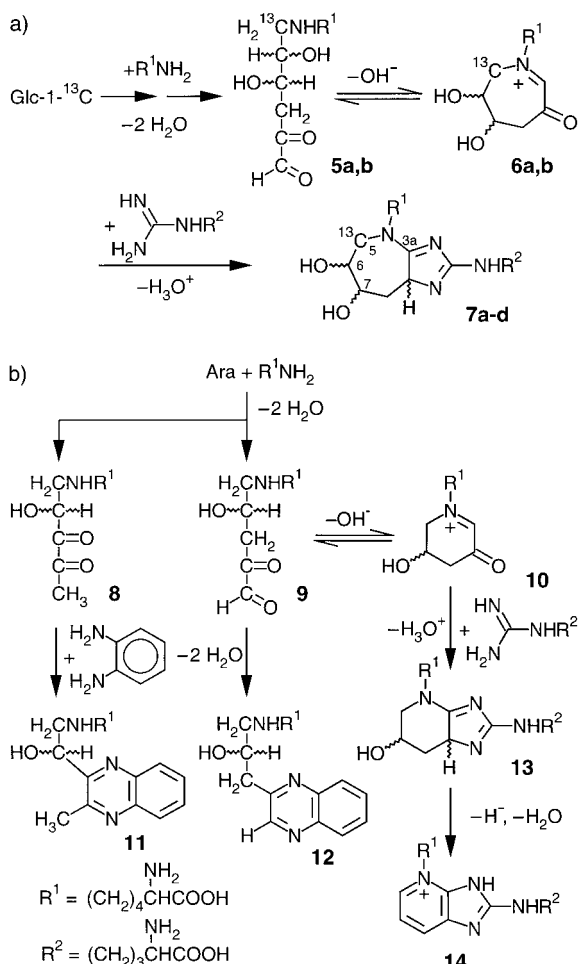
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Scheme 1. The Amadori product 1-deoxy-1-(*N*⁶-lysino)-D-fructose (**1**) and deoxyosones **2–4**, already described in the literature.

with long-term complications of diabetes, atherosclerosis, and Alzheimer's disease.^[1, 6–8] To understand better the impact of the Maillard reaction on these processes and to develop effective therapeutic methods against AGE accumulation in tissues, it is an absolute prerequisite to elucidate the formation pathways of the major protein crosslinks.

We recently reported the formation of the lysine–arginine crosslinks glucosepane (**7**) (Scheme 2a), pentosinane (**13**), and pentosidine (**14**) (Scheme 2b) from the respective carbohydrates and aminoketoses (Amadori products).^[2] None of

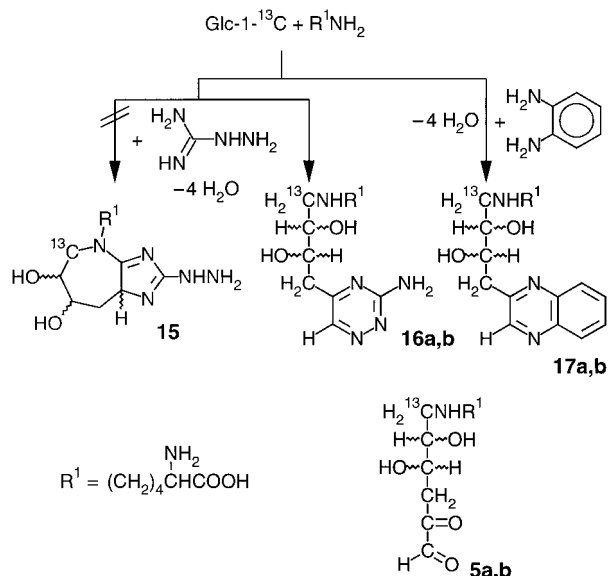


Scheme 2. a) Reaction pathway as established for the formation of the lysine–arginine crosslink glucosepane **7a–d**. b) Identification of the novel pentose-derived dideoxyosones **8** and **9**. Compound **9** very likely undergoes ring closure to form 6-(3-hydroxy-5-oxo-2,3,4,5-tetrahydro-1-pyridinium-yl)norleucine (**10**), which then reacts with an arginine side chain to form pentosinane (**13**) and finally pentosidine (**14**).

these crosslinks can be obtained from authentic 3-deoxyosones such as 3-deoxyglucosone **2** (3-DOG, Scheme 1), even though they are reasonable precursors. A novel pathway thus had to be postulated for generation of **7** from the aminoketose **1** to rationalize how the seven-membered ring in glucosepane is closed.^[2]

In a painstaking study with improved chromatographic techniques, four stereoisomers **a–d** of glucosepane (**7**) could now be separated and unequivocally characterized by means of NMR spectroscopy,^[9a] rather than a single pair **a, b** as reported previously.^[10] This finding cannot be accommodated by the postulated formation pathway, which would give two glucosepane (**7**) isomers only, in which the stereochemistry at C6 and C7 is conserved from the native carbohydrate. Hence, the configuration of one or both of these stereogenic centers must have been lost in the formation of **7**, thus giving rise to four or eight possible diastereoisomers, respectively. As a result of the distance to the *S*-configured stereogenic centers of the amino acids, however, the 6,7,8a-stereoisomers with the same relative but opposite absolute configuration at these three chiral carbon atoms in **7** could neither be separated chromatographically nor resolved by means of NMR spectroscopy.^[9b] With the stereochemical configuration variable at C6,7,8a, only four of the eight possible diastereoisomers of **7** can thus be differentiated.

Incubations with ¹³C-labeled glucose ([1-¹³C]D-glucose) were performed to clarify whether C3a or C5 in **7** derives from C1 of D-glucose. Contrary to our assumption, C5 turned out to be the labeled position, and the postulated pathway^[2] was thus invalid. The results from the reactions of [1-¹³C]D-glucose and lysine with aminoguanidine (AG) instead of arginine were even more surprising. The expected glucosepane analogue **15** (Scheme 3) could not be identified by liquid chromatography–electrospray ionization mass spectrometry (LC–ESI–MS); instead, a twin peak was detected with the quasimolecular ion [*M*+*H*]⁺ at *m/z* 329 and a typical amino-triazine ultraviolet spectrum. NMR spectroscopic analysis



Scheme 3. Identification of the novel dideoxyosone *N*⁶-(2,3-dihydroxy-5,6-dioxohexyl)lysine (**5a,b**).

clearly proved that the compound was N^6 -[4-(3-amino-1,2,4-triazin-5-yl)-2,3-dihydroxybutyl]lysine (**16a,b**; data not shown), and not the triazine derivative of 1,4-dideoxy-1-(N^6 -lysino)-D-hexo-2,3-diulose (**4**). Since AG is an established trapping reagent for α -dicarbonyl compounds, we have clearly identified the new dideoxyosone **5a,b**, which is similar to 3-DOG **2**, with the terminal OH functional group substituted by N^6 of the lysine moiety. To validate this finding, another experiment was performed with *o*-phenylenediamine (OPD) instead of AG to trap **5a,b**. In fact, N^6 -[2,3-dihydroxy-4-(2-quinoxaliny)butyl]lysine (**17a,b**)^[9c] was obtained as a pair of specifiable stereoisomers, analogously to **16a,b**; further diastereoisomers, a result of the *S*-configured stereogenic center of the lysine moiety, could not be differentiated for the reasons stated above. The ^{13}C label appears directly bonded to N^6 of the lysine moiety in both **16a,b** and **17a,b**. Hence, the formation of **5a,b** from aminoketose **1** requires carbonyl shifts along the entire carbohydrate backbone, thus leading to a loss of the original stereochemical configuration at the H-C-OH groups. This pathway is strongly supported by the results of experiments with D_2O as solvent. It was proven by means of LC-ESI-MS and NMR spectroscopy that isotopomers of **17a,b** that incorporate D-C-OH units are obtained; that is, both stereogenic centers have undergone H/D exchange in the course of keto-enol tautomerization. At which stage of the overall reaction sequence water is eliminated from **1** at C4, and whether **4** is an intermediate still needs to be clarified. Derivatives of **4** with primary amine substituents are rather unstable, even as quinoxalines.^[11] Likewise, disaccharides such as lactose (*O*- β -D-galp-(1 $\rightarrow$ 4)-D-glcp) and maltose (*O*- α -D-glcp-(1 $\rightarrow$ 4)-D-glcp) smoothly yield **5a,b**, since the 1 $\rightarrow$ 4 glycoside bond is cleaved in this process by elimination of the *O*-substituent at C4.

In our model incubations, the novel dideoxyosone **5a,b** is formed in larger amounts than is 3-DOG **2**.^[9d] Because **2** has thus far been considered the quantitatively most important deoxyosone both in vivo and in foodstuffs, most investigations hitherto have focused on this compound. The significance of **5a,b** for protein crosslinking in vivo is clear: On the one hand, this lysine-linked α -dicarbonyl compound, which was established first, yields the major crosslink glucosepane (**7a-d**) in the presence of arginine moieties. The formation pathway for **7a-d**, via the intramolecular aldime **6a,b** as plausible intermediate, is given in Scheme 2a. The generation of four distinguishable diastereoisomers of **7** is now easily understood with **5a,b** as precursor. On the other hand, it is unlikely that protein-bound **5a,b** is detoxified by reductase catalysis in vivo in the same way as free 3-DOG **2**,^[12] and thus represents a persistent glycating agent. This hypothesis is strengthened by our investigations into important crosslinks in human serum albumin and lens protein which clearly show that **7** is the dominant compound whereas N^6 -[2-[(4*S*)-4-ammonio-5-oxido-5-oxopentyl]amino]-5-[(2*S*,3*R*)-2,3,4-trihydroxybutyl]-3,5-dihydro-4*H*-imidazol-4-ylidene]-L-lysinate (DOGDIC),^[2] which is derived from 3-DOG **2**, is present only in negligible amounts. The generation of **7a-d** under physiological conditions is remarkable, since this implies a whole sequence of mild enolization and dehydration steps, leading from **1** to **5a,b**. Though often postulated in Maillard chemistry for the

formation of various AGEs,^[1] such long-range shifts of carbonyl groups have not yet been proven. The dideoxyosone **5a,b** is thus not only pivotal in the formation of glucosepane (**7**) but may also be expected to represent the key intermediate for numerous other Maillard products.

The homology between the formation pathways of glucosepane (**7**) and pentosidine (**14**) has prompted us to look for the respective dideoxyosone N^6 -(2-hydroxy-4,5-dioxopentyl)-lysine (**9**) in incubations of arabinose with lysine and OPD (Scheme 2b). N^6 -[2-Hydroxy-3-(2-quinoxaliny)propyl]lysine (**12**) was indeed obtained in good yield from these reaction mixtures, and **9** was thus established as a reasonable precursor of pentosidine (**13**). Further transformation of **13** into pentosidine (**14**) has already been studied in detail.^[2] Unexpectedly, we have also isolated N^6 -[2-hydroxy-2-(3-methyl-2-quinoxaliny)ethyl]lysine (**11**) from these incubations, with a yield three times as high as that for **12**.^[9c] Since no structural homologues to **11** could be detected for hexoses, the formation of dideoxyosones such as N^6 -(2-hydroxy-3,4-dioxopentyl)lysine (**8**) seems to be specific for pentoses.

The results presented above unequivocally establish the novel dideoxyosones **5a,b** and **9** as crucial intermediates in the generation of prominent crosslinks. It is possible, thus, to rationalize the formation of such structures from hexoses or pentoses through a generalized common reaction pathway, paving the way for a better understanding of advanced Maillard processes.

Experimental Section

Chromatographic and spectroscopic procedures: The equipment and methods used for preparative high performance liquid chromatography (HPLC), LC-ESI-MS, and NMR spectroscopy are described in detail in ref. [2] Ammonium formate buffer (10 mM, pH 4.0)–MeOH gradients were employed for all LC separations. Accurate mass determinations were performed with a resolution of 1010 (10% valley definition) and poly(ethylene glycol) 350 monomethyl ether as mass reference. The following scan ranges and reference peaks were used for calibration: **17a,b** (m/z 335–435); m/z 341.2175, 358.2441, 385.2438, 402.2703, 429.2700; **11** and **12** (m/z 290–390); m/z 297.1913, 314.2179, 341.2175, 358.2441, 385.2438.

7a-d: The synthesis with native D-glucose and the isolation of the *tert*-butoxycarbonyl (*t*Boc) derivatives of **7** as well as the removal of the *t*Boc groups was performed as described in ref. [10] The two crude products obtained were purified by means of preparative HPLC (gradient: % MeOH (t [min]) 0(0)–5(5–7)–0(8–13); detection at 254 nm). Fractions with t_R = 5.4, 6.2, 7.7, and 8.9 min yielded, after lyophilization, **7c**·3HCOOH (7.0 mg, 0.012 mmol, 0.3%), **7a**·3HCOOH (24.3 mg, 0.043 mmol, 1.1%), **7b**·3HCOOH (14.9 mg, 0.026 mmol, 0.7%), and **7d**·3HCOOH (4.7 mg, 0.008 mmol, 0.2%), respectively. Preparation (scaled down to one quarter) was repeated with [^{13}C]D-glucose (Cambridge Isotope Laboratories Inc., Andover, MA, USA), and the products were isolated analogously.

17a,b, 11, and 12: D-Glucose (360 mg, 2 mmol) or D-arabinose (300 mg, 2 mmol), N^6 -*t*Boc-L-lysine (1.47 g, 6 mmol), *o*-phenylenediamine (430 mg, 4 mmol), diethylenetriaminepentaacetic acid (5 mg, 0.013 mmol), and phosphate buffer (1.6 g, 1 mmol, pH 7.4) were dissolved in water (10 mL). Each mixture was flushed with argon, kept at 70 °C for 2 d, and purified by means of preparative HPLC (gradient: % MeOH (t [min]) 5(0)–70(20)–100(22–25)–5(28–35); detection at 318 nm). Fractions with t_R = 19.9 min (incubation with D-glucose), t_R = 20.1 and 20.9 min (incubation with D-arabinose) were lyophilized, dissolved in HCl (3N, 2 mL), and kept at ambient temperature for 30 min. The pH value was adjusted to 7 by slowly adding solid NaHCO_3 , the volume was finally filled up to 4 mL, and the solution was subjected to preparative HPLC (gradient: % MeOH (t [min]) 5(0)–55(12)–100(15–18)–5(20–25); detection at 318 nm). For the D-glucose

incubation, the fraction with $t_R = 10.0$ min yielded, after lyophilization, **17a,b**·HCOOH (unlabeled, 36.5 mg, 0.089 mmol, 4.5 %), LC-ESI-MS (gradient: % MeOH (t [min]) 5(0)-95(30-35)-5(40-45), cone voltage 40 V). **17a**: $t_R = 8.3$ min; m/z (%): 401 (3) [MK]⁺, 385 (4) [MNa]⁺, 363 (100) [MH]⁺, 219 (8), 187 (17); **17b**: $t_R = 8.5$ min; m/z (%): 401 (4) [MK]⁺, 385 (6) [MNa]⁺, 363 (100) [MH]⁺, 219 (12), 187 (14); accurate mass (mean of 11 measurements $\pm$ standard deviation): **17a,b**: calculated for C₁₈H₂₇N₄O₄: 363.2032, found: m/z 363.2034 $\pm$ 0.0007 [MH]⁺. Preparation (scaled down to one seventh) was repeated with [1-¹³C]D-glucose, and the products were isolated analogously. For the D-arabinose incubation, fractions with $t_R = 10.5$ and 11.3 min yielded, after lyophilization, **11**·HCOOH (12.3 mg, 0.033 mmol, 1.6 %) and **12**·HCOOH (4.8 mg, 0.013 mmol, 0.6 %), respectively, LC-ESI-MS (for gradient and cone voltage, see above). **11**: $t_R = 7.5$ min; m/z (%): 371 (1) [MK]⁺, 355 (2) [MNa]⁺, 333 (45) [MH]⁺, 175 (100), 159 (30); **12**: $t_R = 8.3$ min; m/z (%): 371 (1) [MK]⁺, 355 (1) [MNa]⁺, 333 (100) [MH]⁺, 315 (5), 189 (5), 187 (4); accurate mass (mean of 10 measurements $\pm$ standard deviation): **11**: calculated for C₁₇H₂₅N₄O₃: 333.1927, found: m/z 333.1931 $\pm$ 0.0007 [MH]⁺; **12**: calculated for C₁₇H₂₅N₄O₃: 333.1927, found: m/z 333.1935 $\pm$ 0.0010 [MH]⁺.

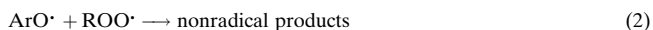
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- [9] See Supporting Information for: a) ¹H and ¹³C NMR data for **7a–d**, (Table 1); b) reasoning for the number of observable diastereoisomers for **7** and assignment of their relative configuration (Tables 1 and 2 and Figure 1); c) ¹H and ¹³C NMR data for **17a,b** (Table 3); d) LC chromatograms (Figure 2); e) ¹H and ¹³C NMR data for **11** and **12** (Table 3).
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A Method for Thermal Generation of Aryloxy Radicals at Ambient Temperatures: Application to Low-Density Lipoprotein (LDL) Oxidation**

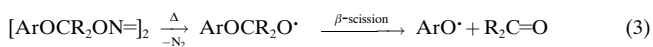
Thomas Paul* and Keith U. Ingold*

Antioxidant phenols (ArOH) react with peroxy radicals (ROO•) and form relatively unreactive aryloxy radicals (ArO•) [Eq. (1)] which, in homogeneous solutions, then trap a second peroxy [Eq. (2)].^[1, 2] α -Tocopherol (TocH, vitamin E) is the most active lipid-soluble antioxidant in



mammals^[2] but, surprisingly, it acts as a prooxidant in human low-density lipoproteins (LDL).^[3] Oxidatively modified LDL may initiate atherosclerosis.^[4] Various agents (e.g., enzymes, transition metals) have been suggested to be responsible for this modification of LDL in vivo.^[5] The free radical initiated oxidation of LDL in which TocH transfers radical character from water-soluble peroxy radicals into the LDL has been studied extensively. The resulting tocopheroxyl radical (Toc•) then carries a lipid peroxidation chain within the LDL in a process christened tocopherol-mediated peroxidation (TMP).^[6] The aryloxy radical, tyrosyl, which is formed (in 25 % yield) by reaction of myeloperoxidase with tyrosine during the immune response, can also initiate LDL peroxidation.^[7] These two examples of aryloxy radical-induced biological damage highlight the need for quantitative, in vitro studies of their reactions using thermolabile compounds which would provide “clean” and well-defined ArO• fluxes. To design an aryloxy radical thermal source (ARTS) which would generate *any* ArO• and *only* that ArO• radical is therefore a worthwhile and exciting challenge.^[8]

Hyponitrites, which are not subject to metal ion- or radical-induced decomposition,^[9, 10] decompose at ambient temperatures to give N₂ and alkoxyl radicals. It appeared probable that aryloxyalkoxyl radicals would undergo very fast β -scission^[11] to yield aryloxy radicals [Eq. (3)]. A synthetic route to aryloxyalkyl hyponitrites suitable for many different



[*] Dr. T. Paul,^[+] Dr. K. U. Ingold
National Research Council of Canada
100 Sussex Drive
Ottawa, ON, K1A 0R6 (Canada)
Fax: (+1) 613-941-8447
E-mail: Thomas.Paul@avecia.com, Keith.Ingold@nrc.ca

[+] Current Address:
Avecia Ltd., P.O. Box 42, Hexagon House
Blackley, Manchester, M9 8ZS (UK)
Fax: (+44) 161-721-5240

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may be formed during **3b** decomposition the true value of e is likely to be $>5\%$.

The phenoxyl radical could not be detected during the thermal decomposition of **3a** at 23°C , presumably because the $\text{PhO}^\bullet/\text{PhO}^\bullet$ reaction ($2k = 1 - 12 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$)^[16] is so much faster than the $\text{Toc}^\bullet/\text{Toc}^\bullet$ reaction.^[14] However, e for **3a**, could be estimated by assuming that the in-cage reaction of **4sc** would yield equal amounts of **5a** and **PhOH** whereas GC analysis showed an excess of **PhOH** and biphenols over **5a**. From the “excess” phenol, e was estimated to be around 20% .

The aryloxy radical-initiated peroxidation of LDL was chosen to illustrate a biologically relevant in vitro application of **ARTS**. To a freshly prepared LDL dispersion **3a** was added and incubated at 37°C until decomposition was virtually complete. The TocH consumption curve and the cholesteryl ester hydroperoxide (CEOOH) formation curve are characteristic of **TMP** in that peroxidation is faster while TocH is present than after the TocH is consumed^[6] (Figure 2).

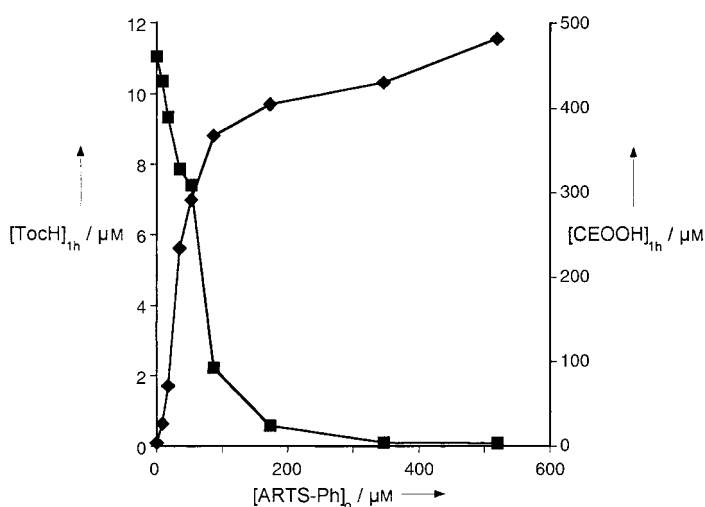
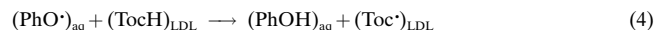


Figure 2. Concentration of cholesteryl ester hydroperoxides (CEOOH) ($\blacklozenge$) and α -tocopherol ($\blacksquare$) in $1.8 \mu\text{M}$ LDL dispersed in aerated phosphate buffered saline (PBS; pH 7.4, 50 mM) after incubation for 1 h at 37°C in the presence of the indicated initial **ARTS-Ph** concentrations. **ARTS-Ph** was added as a solution in DMSO, the amount of which did not exceed 1% of the $300 \mu\text{L}$ LDL dispersion.

Furthermore, at low initial **3a** concentrations where significant amounts of TocH remain after the 1 h incubation, the CEOOH was formed in a chain reaction, for example $d[\text{CEOOH}]/d[\text{PhO}^\bullet] \approx 16$ at an initial $[\mathbf{3a}] = 35 \mu\text{M}$ (see Supporting Information). That is, **TMP** is initiated in LDL by $\text{PhO}^\bullet$ attack on TocH [Eq. (4)]. **TMP** explains the earlier



observation that tyrosyl radicals generated by myeloperoxidase initiate LDL peroxidation in a process not inhibited by TocH .^[7b]

At low **3a** concentration, approximately 0.2 molecules of TocH are consumed per $\text{PhO}^\bullet$ generated (see Supporting Information). This value would be 0.5 if all the $\text{PhO}^\bullet$ were destroyed by TocH and it implies that $\text{PhO}^\bullet/\text{PhO}^\bullet$ coupling reactions are probably important under the present conditions.

Aryloxy radical induced oxidative stress has been largely ignored because of the lack of suitable precursors. The present synthesis of two **ARTS** overcomes this lack and provides a new tool for studying the effects of known fluxes of $\text{ArO}^\bullet$ radicals on biologically relevant targets. Currently, we are designing a synthesis for water-soluble **ARTS**s which will enable the tyrosyl radical to be generated in a controlled manner.

Experimental Section

The $\text{Toc}^\bullet$ EPR spectrum was recorded at room temperature under N_2 on a Varian E104 spectrometer (9.5 GHz) with microwave power = 2 mW, modulation amplitude = 0.04 mT, modulation frequency = 100 kHz, scan time = 8 min. The hyperfine splitting constants were obtained using the ESR simulation program WINSIM.^[17] NMR spectroscopic data were recorded on a Bruker 400-DRX spectrometer. Freshly isolated LDL,^[18] was dispersed in aerated PBS, mixed with a known amount of a **3a** stock solution in DMSO and then incubated for 1 h at 37°C with the usual analyses for CEOOH and TocH .^[19]

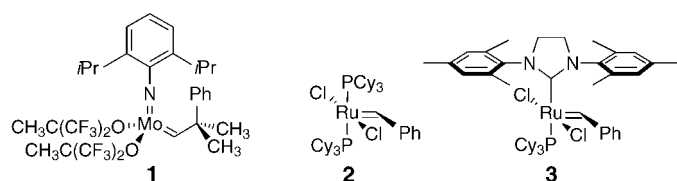
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A One-Pot Cross-Metathesis/Allylboration Reaction: A Three-Component Coupling for the Synthesis of Functionalized Homoallylic Alcohols**

Steven D. Goldberg and Robert H. Grubbs

The development of methods for the chemo- and stereoselective formation of carbon–carbon bonds remains a primary goal of organometallic and organic chemistry. The olefin metathesis reaction^[1] has become such a method, partly as a result of the development of well-defined transition metal alkylidene catalysts, such as the molybdenum alkylidene **1**^[2] and the ruthenium benzylidene **2** (Scheme 1).^[3] In particular,

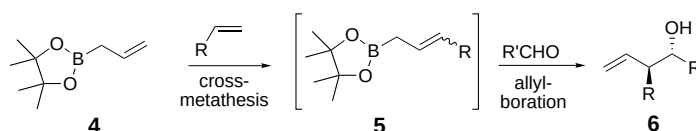


Scheme 1. Olefin metathesis catalysts.

2 is characterized by its remarkable stability to various functional groups and activity under mild reaction conditions. Recently, olefin cross-metathesis has emerged as a versatile method for the synthesis of functionalized acyclic structures.^[1, 4] The discovery of highly active N-heterocyclic carbene-containing catalysts,^[5] for example, **3**,^[6] has advanced the utility of cross-metathesis, thus allowing the synthesis of small molecules with a wide range of pendant functional groups, including α,β -unsaturated carbonyl compounds,^[7] styrenes,^[8] vinyl and allyl phosphonates,^[9] vinyl^[7] and allyl silanes,^[10] vinylloxiranes,^[7] and trisubstituted olefins.^[11] Consequently, olefin cross-metathesis presents a unique opportunity to introduce reactive functional groups, not as structural elements, but for use in subsequent mechanistically distinct carbon–carbon bond-forming reactions.

The allylation of aldehydes with allyl boron reagents is an excellent method for the stereoselective synthesis of homoallylic alcohols and is widely used in organic synthesis.^[12] Studies by the groups of Hoffmann,^[13] Roush,^[14] and Brown^[15] provided a detailed understanding of this transformation and resulted in the development of high-yielding, enantio- and diastereoselective allylboration protocols.^[13–15] Despite decades of interest, the accessibility of functionalized allyl boron

reagents remains limited. Traditionally, these complexes are prepared by allylmethyl addition to haloboranes^[16] or trialkoxy boranes,^[14a] vinylmetal addition to halomethyl boranes,^[17] or by hydroboration of 1,3-dienes;^[18] methods that may be incompatible with complex substrates and/or many desirable functional groups. Recently, allyl boronates have been prepared by using transition metal mediated processes,^[19] yet these methods are limited in their substrate scope^[19b–d] or require stoichiometric amounts of tin reagents,^[19a] and there remains no general method for the construction of allyl boronates with allylic functionality. Olefin metathesis appears ideally suited to address this problem. Herein we report a one-pot cross-metathesis/allylboration sequence that affords densely functionalized homoallylic alcohols (Scheme 2). This three-component coupling reaction combines two orthogonal, chemoselective, and mild carbon–carbon bond-forming reactions and demonstrates the power of olefin metathesis for the preparation of novel and highly reactive reagents.



Scheme 2. One-pot cross-metathesis/allylation reaction.

The dimerization of pinacol allyl boronate (**4**)^[20] was investigated to determine its compatibility with catalysts **2** and **3**. Treatment of **4** with catalyst **2** (5 mol %) in dichloromethane (0.2 N) at 40 °C for 12 h furnished the corresponding dimer **5** ($R = \text{CH}_2\text{B}[\text{OC}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2\text{O}]$) as the major product in a 1.5:1 *E*:*Z* mixture. To our surprise, attempts to dimerize **4** by using the more active catalyst **3** gave only trace amounts of the desired dimer, thus generating a complex mixture of products, composed, in part, of vinyl boronates formed by olefin isomerization.^[21]

Auspiciously, the inclusion of an olefin cross partner in the above reactions results in productive cross-metathesis to afford functionalized allyl boronates **5**. This finding demonstrates that productive cross-metathesis with either **2** or **3** is competitive with the olefin isomerization discussed above. Although these reactions may be monitored by means of thin-layer chromatography, significant hydrolysis of the boronate esters **5** occurs during purification by silica gel chromatography. However, addition of an aldehyde to the crude cross-metathesis reaction mixtures furnishes the corresponding homoallylic alcohols **6**, thus revealing that purification of the intermediates **5** is unnecessary and that the catalysts do not interfere with allylboration. This one-pot protocol has been applied to the preparation of a variety of functionalized homoallylic alcohols (Tables 1–3).^[22]

The effects of varying the catalyst and the relative stoichiometries of the components of the cross-metathesis/allylation reaction were explored by using (*Z*)-1,4-diacetoxy-2-butene and benzaldehyde (Table 1).^[23] *E* allyl boronates afford *anti*^[24] products with high diastereoselectivity,^[13b] and catalyst **3** is more *E* selective than catalyst **2** in olefin metathesis reactions,^[1, 25] thus suggesting that catalyst **3** may

[*] Dr. S. D. Goldberg, Prof. R. H. Grubbs
Arnold and Mabel Beckman Laboratories of Chemical Synthesis
Division of Chemistry and Chemical Engineering
California Institute of Technology
Mail Code 164-30, Pasadena, CA 91125(USA)
Fax: (+1) 626-564-9297
E-mail: rhg@its.caltech.edu

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provide homoallylic alcohol **6a** with greater *anti* selectivity. Not only does this prediction hold true, but the yield of **6a** is significantly greater when catalyst **3** is used (Table 1, entries 1 and 2). The catalyst loading could be reduced to 2 mol %

Table 1. Cross-metathesis/allylation with pinacol allylboronate (**4**) and (Z)-1,4-diacetoxy-2-butene.

Entry	Cross partner [equiv]	Benzaldehyde [equiv]	Catalyst (mol %)	Yield [%]	<i>anti:syn</i> ^[a]
1	3	1.5	2 (5)	32	1.8:1
2	3	1.5	3 (5)	75	4.5:1
3	3	1.5	3 (2)	75	4.5:1
4	0.5	1.5	3 (5)	57	4.7:1
5	3	0.75	3 (5)	75	4.5:1

[a] Ratios determined by means of ¹H NMR spectroscopy.

(Table 1, entry 3) without affecting the yield or the diastereoselectivity. The fact that alcohol **6a** is formed in 57 % yield when using stoichiometric amounts of the cross partner (Table 1, entry 4), greater than is expected statistically (50 %), suggests that the mixed cross product **5** (R=CH₂OAc) is favored over the respective symmetrical dimers. Interestingly, with benzaldehyde as the limiting reagent (Table 1, entry 5), the yield of **6a** is undiminished (75 %), which implies that the cross-metathesis step is not yield-determining in this case.

Homoallylic alcohols with protected hydroxymethyl,^[26] protected aldehyde and halomethyl side chains may be prepared efficiently by using the developed protocol (Table 2). As stated above, a decrease in the catalyst loading does not affect the overall chemical yield (Table 2, entries 2–5),

and only in entry 2 is a noticeable decrease in the *anti:syn* ratio observed. Silyl^[27] and benzyl allylic ethers are efficiently transformed into the corresponding homoallylic alcohols **6b** and **6c**, respectively, thus allowing facile tuning of the olefinic substrate to conform with preexisting protecting group strategies (Table 2, entries 1 and 2). 2-Vinyl-1,3-dioxolane is effectively converted into alcohol **6d** in 69 % yield as a single diastereomer (Table 2, entry 3), in agreement with the expectation that increasing steric bulk at the allylic carbon atom would favor the formation of *trans* olefins.^[28] In contrast, terminal olefins that lack allylic functional groups are poor substrates for this reaction and afford products in low yields and with lower *anti:syn* ratios.

The direct incorporation of a halomethyl group by allylboronation (or by the related aldol addition reaction) had not previously been reported. The current protocol allows the synthesis of bromomethyl (Table 2, entry 4) and chloromethyl (Table 2, entry 5) allylation products **6e** and **6f**, respectively, in good yields from the corresponding 1,4-dihalo-2-butenes.^[29] This sequence effectively constitutes the first preparation of a β-halo anion equivalent, thus allowing the synthesis of halogenated targets that would require several steps to prepare by traditional methods.

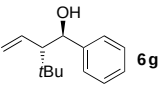
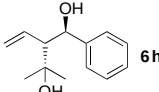
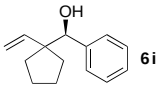
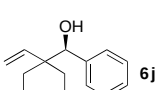
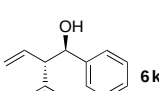
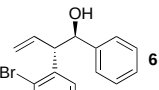
In light of the moderate *anti:syn* ratios obtained with smaller allylic functional groups, we explored olefinic substrates known to form predominantly *trans* products in cross-metathesis reactions (Table 3). Neopentyl olefins (Table 3, entries 1 and 2),^[30] 1,1-disubstituted olefins that ultimately afford products containing quaternary centers (Table 3, entries 3 and 4), and styrenes (Table 3, entries 5 and 6) are successful in this sequence. For these substrates, a decrease in the loading of catalyst **3** lowers the yield of **6g** considerably (Table 3, entry 1). Importantly, the loading of the terminal olefin component in these cases is increased significantly beyond that used in the previous examples. This requirement

Table 2. Cross-metathesis/allylation reactions with functionalized olefins.

Entry	Cross partner	3 [mol %]	Yield [%]	<i>anti:syn</i> ^[a]	Product
1		5	44–67	4:1	
2		5 2	60 63	4.7:1 3.2:1	
3		5 2	68 69	> 20:1 > 20:1	
4		5 2	73 72	3.8:1 3.6:1	
5		5 2	78 79	4.9:1 4.6:1	

[a] Ratios determined by means of ¹H NMR spectroscopy.

Table 3. Cross-metathesis/allylation with hindered olefins and styrenes.

Entry	Cross partner	Equiv	3 [mol %]	Yield [%]	Product ^[a]
1		5	5	35	
		20 ^[b]	5	51	
		30 ^[b]	2	17	
2		3	5	49	
		10	5	58	
3		10	5	34	
		20 ^[b]	5	66	
4		20 ^[b]	5	45	
5		5	5	25	
6		10	5	60	

[a] All products formed in >20:1 *anti:syn* ratio (determined by means of ¹H NMR spectroscopy). [b] The cross partner was used as solvent.

results from the formation of vinyl boronates through olefin isomerization (see above) becoming competitive with productive cross-metathesis for these less reactive cross partners.^[31]

In conclusion, the successful application of olefin cross-metathesis to the preparation of functionalized allyl boronate reagents has resulted in a one-pot three-component coupling procedure for the synthesis of functionalized homoallylic alcohols. Of particular interest is the direct incorporation of halomethyl side chains, as can be seen in the previously unknown γ -halo allyl boronates **6e** and **6f**. This methodology highlights the utility of olefin metathesis for the synthesis of highly functionalized and reactive reagents that would be challenging or impossible to prepare by traditional methods.

Experimental Section

General procedure: A flame-dried round-bottomed flask was charged with **4** (1 equiv) and the olefin cross partner (3.0 equiv). A rubber septum was attached, dichloromethane was added (0.2–0.3 N in **4**), and argon was bubbled through the resultant solution for 10 min. Under a stream of argon, **3** (0.050 equiv) was added to the degassed solution as a solid. A reflux condenser was attached immediately, and the entire system was flushed with argon for 2 min. The colored solution was then heated at reflux for 2–12 h, and the reaction was monitored by thin-layer chromatography. Upon consumption of **4**, the aldehyde (1.5 equiv) was added to the reaction mixture through a syringe, and the resultant solution was stirred at 23 °C for 12–48 h. The solution was concentrated in vacuo, and the residue was purified by means of silica gel chromatography to afford **6**. Characterization data for **6a–6l** are given in the Supporting Information.

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- Pinacol allyl boronate was employed for its ease of synthesis and stability to elevated temperature and to long-term storage.
- Olefin isomerization has been observed during ring-closing metathesis reactions with ruthenium benzylidene catalysts; see: a) A. Fürstner, O. R. Thiel, L. Ackermann, H.-J. Schanz, S. P. Nolan, *J. Org. Chem.* **2000**, *65*, 2204; b) S. S. Kiderman, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, F. P. J. T. Rutjes, *Org. Lett.* **2001**, *3*, 2045; c) L. A. Paquette, I. Efremov, *J. Am. Chem. Soc.* **2001**, *123*, 4492.
- Varying the reaction temperature (23 °C or 60 °C) or the solvent did not increase the yield or the *anti:syn* ratio of the products.
- Our investigation focused on the synthesis of allyl boronate reagents by means of olefin metathesis, not on the effect of the aldehyde component, which has been aptly studied elsewhere. Therefore, for

consistency, benzaldehyde was used exclusively as the aldehyde component in these reactions.

- [24] *Anti* refers to the relative stereochemistry of the hydroxy and side-chain groups, for example, product **6a** as drawn.
- [25] C. W. Lee, R. H. Grubbs, *Org. Lett.* **2000**, 2, 2145.
- [26] Wuts et al. were first to prepare the analogous THP-protected (THP = tetrahydropyran) hydroxymethyl products by means of allylboration; see ref. [17b].
- [27] This substrate isomerizes to the corresponding silyl enol ether under the reaction conditions, resulting in the varying yields of **6b**: C. W. Lee, R. H. Grubbs, unpublished results.
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- [30] A. K. Chatterjee, R. H. Grubbs, unpublished results.
- [31] This is in stark contrast to previous studies in which hindered olefins could be used in nearly equal stoichiometric amounts with terminal olefins as a result of the slow dimerization of the hindered substrates; see ref. [11].

Electrodeposition of Redox Polymers and Co-Electrodeposition of Enzymes by Coordinative Crosslinking**

Zhiqiang Gao, Gary Binyamin, Hyug-Han Kim, Scott Calabrese Barton, Yongchao Zhang, and Adam Heller*

The electrodeposition of metals and electron- or hole-conducting polymers proceeds through forming metallic or covalent bonds, respectively. We show here that films of hydrated redox polymers can also be electrodeposited. Electron conduction in redox polymers derives of the mobility of their segments. When the polymers are hydrated, their mobile segments randomly collide. Upon colliding, reduced mobile segments transfer electrons to oxidized ones.^[1–9] The electrodeposition of redox polymers results of the formation of coordinative bonds that crosslink the chains.

The electrodeposited polymers were water soluble and comprised backbone-bound ligands and Os²⁺/Os³⁺ complexes with exchangeable Cl[–] ions in their inner coordination sphere. When the polymers were adsorbed on electrodes and were electroreduced, they were crosslinked by ligand exchange: about 5–10% of the labile Cl[–] ions of the Os complexes of one polymer chain were exchanged by the more strongly coordinating pyridine or imidazole functions of neighboring chains.

[*] Prof. A. Heller, Dr. Z. Gao, Dr. G. Binyamin, Dr. H.-H. Kim, Dr. S. C. Barton, Y. Zhang
Department of Chemical Engineering and Texas Materials Institute
The University of Texas
Austin, TX 78712 (USA)
Fax: (+1) 512-471-8799
E-mail: heller@che.utexas.edu

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It is well known that transition metal ions exchange ligands when electroreduced and/or electrooxidized.^[10–14] It is also known that upon illumination the redox polymer formed by coordinating [Ru(bpy)₂Cl]⁺/[Ru(bpy)₂Cl]²⁺ to poly(4-vinylpyridine) exchanges its inner-sphere chloride with water, perchlorate or acetonitrile.^[15] Here we show that when the initially reversibly adsorbed water-soluble redox polymers are electrochemically cycled, they are irreversibly crosslinked and are thereby irreversibly electrodeposited. The resulting films conduct electrons when they are hydrated, and their redox segments are mobile enough to collide, even though they are tethered to the crosslinked polymer. The deposition is rapid (200 s) and takes place at 25 °C in aqueous solutions at neutral pH. As the crosslinking caused by ligand exchange proceeds under mild conditions, dissolved enzymes with amine or heterocyclic nitrogen functions coordinating transition metals are conveniently co-electrodeposited. Substrates of the enzymes are electrocatalytically oxidized/reduced on the resulting “wired enzyme” electrodes.^[16, 17]

The ligand exchange, and therefore the electrodeposition, takes place only when the surface coverage by the precursor redox polymer is high. When the precursor polymer does not densely cover the surface, the likelihood of finding neighboring chains at distances short enough for ligand exchange is small. Chloride, a weakly coordinating anionic ligand, is exchanged when Os³⁺ is electroreduced to Os²⁺ thereby diminishing the coulombic component of the binding energy. As the rate of interchain ligand exchange increases with the surface density of the chain containing the exchanged ligand and with that of the chain containing the exchanging ligand, it scales superlinearly with the surface density of the adsorbed polymer. At high surface coverage, the crosslinking is expected to be rapid and at low coverage it is expected to be negligible. The surface density of adsorbed redox polymer can be modulated on vitreous carbon electrodes through their oxidation, because oxidation of the carbon surface adds polycation-binding carboxylate and phenolate functions.^[18]

On vitreous carbon electrodes that were pre-oxidized in plasma (air, 1 Torr, 5 min) the redox polymers were electrodeposited under exceptionally mild conditions, merely by cycling the electrodes between –150 and +150 mV vs the polymer's redox potential. When the vitreous carbon electrodes were not oxidized in plasma, the electrodeposition required electrooxidation of their surfaces and did not proceed unless the electrodes were cycled to greater than +0.4 V prior to applying the crosslinking reducing potential. The rate of deposition increased when the oxidizing potential was raised up to 0.8 V (vs Ag/AgCl; Figure 1). Thus, the purpose of the oxidative half cycle, where the electrode surface is oxidized, is to increase the surface density of the redox polymer prior to its crosslinking in the reductive half cycle.

Crosslinked films of redox polymer **I** (Scheme 1) were irreversibly electrodeposited from redox polymer solutions in PBS (0.5–1.0 mg mL^{–1} polymer, pH 7.1, 20 mM phosphate buffer, 0.1 M NaCl solution). In the 200-s process the potential was stepped 50 times between –0.3 (2 s) and +0.8 V (2 s). A sequence of the applied square potential waves is illustrated in

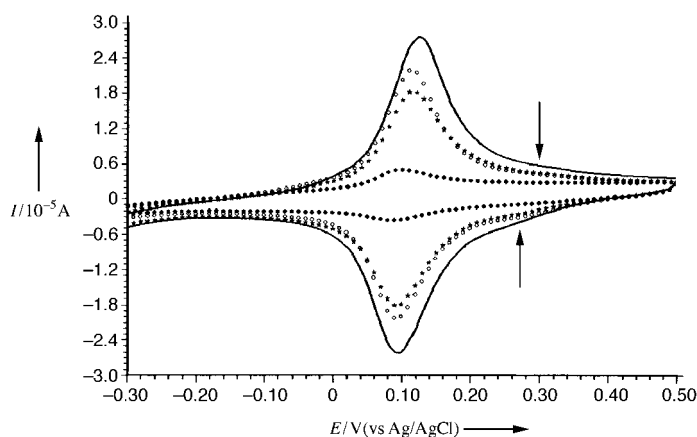


Figure 1. Dependence of the cyclic voltammograms of **I** on the oxidizing potential applied in its deposition. The reducing potential was fixed at -0.3 V. Oxidizing potential: 0.40 (●), 0.60 (*), 0.70 (○), and 0.80 V (—). pH 7.1, PBS buffer, 100 mV s^{-1} , 50 square waves. Note the difference between the left and right branches of the voltammetric waves, resulting of the formation of crosslinking $\text{Os}^{2+/3+}$ centers, the redox potential of which is higher. The approximate positions of the peaks of the waves of the crosslinking centers are marked with arrows.

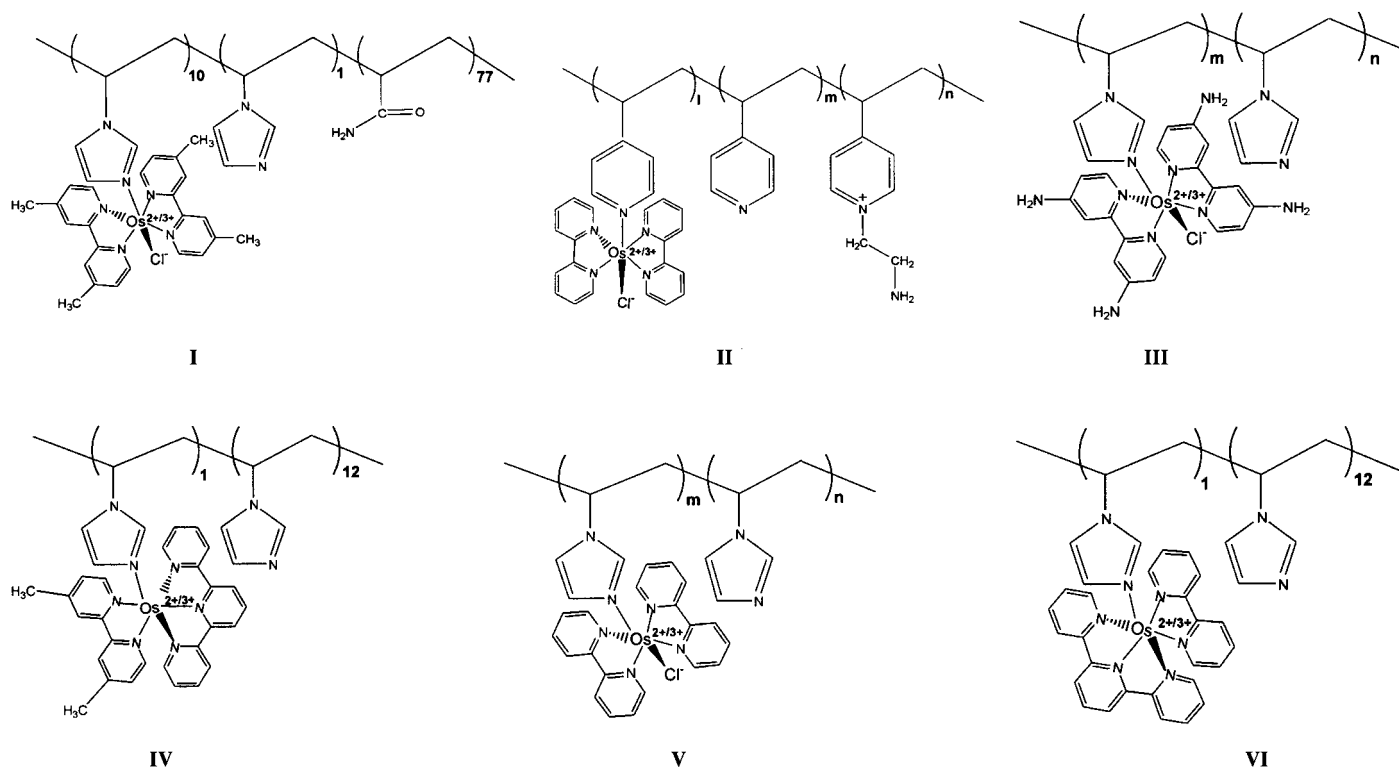
the insert of Figure 3. In the case of redox polymer **I**, integration of the cyclic voltammograms showed coverage by about $10^{-9} \text{ mol redox centers per cm}^2$. The exchange of Cl^- by imidazole or pyridine added small, embedded voltammetric waves, making the tails of the voltammograms of the electrodeposited films asymmetrical: The currents of their positive (right-side) branches exceeded those of their negative (left-side) branches.

Because the crosslinking Os centers have six heterocyclic nitrogen atoms in their inner coordination sphere, their redox

potential is shifted to more positive values relative to the potential of the noncrosslinking Os centers, which remain coordinated by Cl^- and five heterocyclic nitrogen atoms. The shift is about 200 mV when the exchanging ligand is an imidazole function and about 250 mV when the exchanging ligand is a more strongly coordinating pyridine function.^[19, 20] The approximate positions of the embedded peaks associated with the Os centers coordinated by six nitrogen atoms are marked in Figures 1 and 2 by arrows. The maximal current difference between the right and left branches of the voltammograms (associated with the centers coordinated by six nitrogen atoms) and the peaks associated with the centers coordinated by five nitrogen atoms and one chloride shows that upon electrodeposition about $5\text{--}10\%$ of the Os centers exchanged Cl^- ions by heterocyclic nitrogen atoms.

The waves of the voltammograms of the freshly electrodeposited films of **I** narrowed in the first 20 electrooxidation/reduction cycles. Their peak heights increased linearly with the scan rate up to 500 mV s^{-1} ; at small scan rates the peaks of the reduction and oxidation waves were separated by less than 10 mV (Figure 2).^[21] When **I** was electrodeposited from its solution in PBS (0.5 mg mL^{-1}), the thickness of the electroactive films increased linearly with the number of cycles in the first 50 (2+2)-s cycles; it increased less and nonlinearly between 50 and 200 cycles; and at >200 cycles the thickness no longer increased (Figure 3).

As seen from Table 1, persistent films were electrodeposited only from solutions of those redox polymers that contain uncoordinated imidazole or pyridine ligands and Os complexes with inner-sphere Cl^- : Polymers **IV** and **VI** have no inner-sphere Cl^- and are not deposited; polymers **I**, **II**, **III**, and **V** do have inner-sphere Cl^- and are electrodeposited.



Scheme 1. Structures of the redox polymers studied.

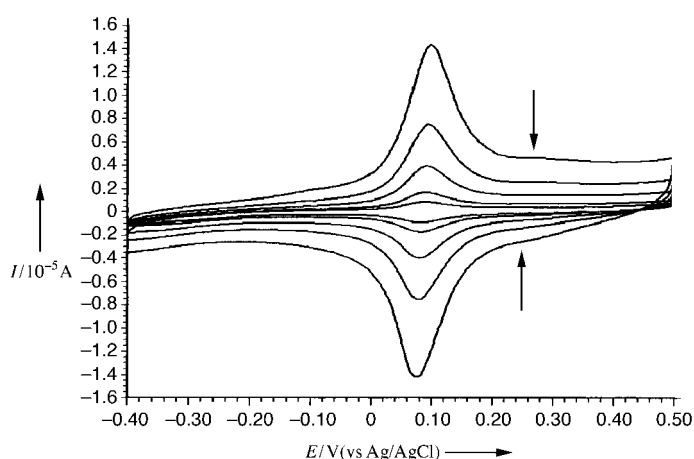


Figure 2. Cyclic voltammograms of the fully annealed film of **I** on vitreous carbon. pH 7.1, PBS buffer. Scan rates from the innermost to the outermost waves: 10, 20, 50, 100, and 200 mVs⁻¹. The approximate positions of the peaks of the waves of the crosslinking centers are marked with arrows.

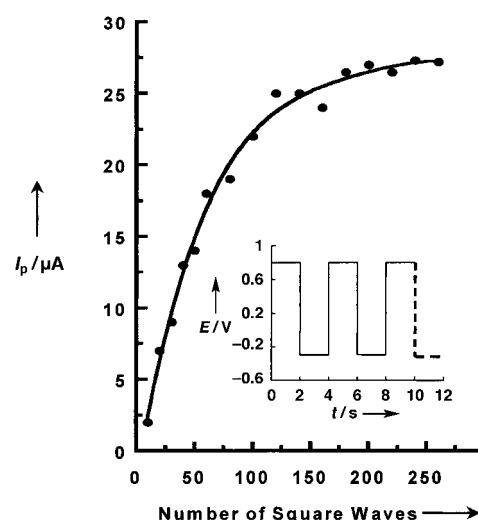


Figure 3. Dependence of the voltammetric peak current I_p on the number of square waves applied. Insert: A sequence of the square potential waves applied in the electrodeposition.

It had been recognized earlier that Ru²⁺ complexes containing labile ligands, for example aqua complexes, are readily bound to proteins by exchanging their labile ligand with a protein-bound histidine.^[22–24] Because histidine, lysine, and arginine functions coordinate also to Os²⁺/Os³⁺, enzymes were readily co-electrodeposited with the redox polymers. Co-electrodeposition of redox polymers (0.50 mg mL⁻¹) and glucose oxidase (GOX), horseradish peroxidase (HRP), soybean peroxidase (SBP), or laccase (0.50 mg mL⁻¹) at room temperature from solutions with pH (7.2 ± 0.1) yielded electrocatalytic films, on which the substrates of the enzymes were selectively electrooxidized/reduced. Thus glucose was electrooxidized on electrodes with **I** and co-deposited GOX;^[25] H₂O₂ was electroreduced on electrodes with **I** and co-deposited HRP or SBP; and O₂ was electroreduced on electrodes with co-deposited laccase. The cyclic voltammograms of the GOX and the SBP electrodes are shown in Figure 4. As in the case of the pure redox polymer films, the redox polymer–enzyme films also have rapidly electron-exchanging redox couples: At scan rates up to 100 mVs⁻¹, the separation of the peaks of the voltammetric electroreduction and electrooxidation waves is less than 10 mV for the enzyme electrodes, and almost no hysteresis is observed at a scan rate of 10 mVs⁻¹ (Figure 4).

To prove that the glucose oxidase was coordinatively bound to the redox polymer, not entrapped in it, an ultrathin (about

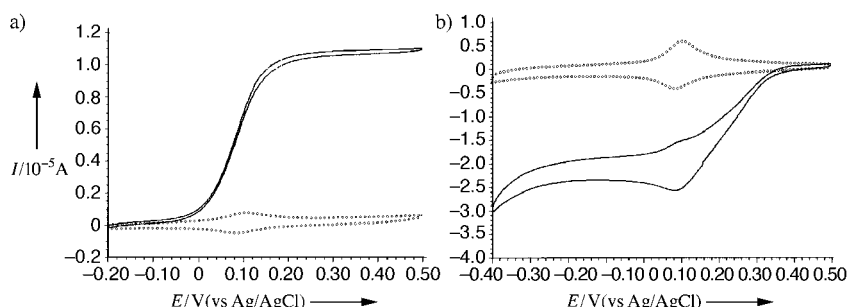


Figure 4. a) Cyclic voltammograms of **I** with co-electrodeposited GOX in PBS buffer: no glucose (○), 20 mM glucose (—). b) Cyclic voltammograms of **I** with co-electrodeposited SBP in PBS buffer: no H₂O₂ (○), 1.0 mM H₂O₂ (—). 3-mm vitreous carbon electrodes, pH 7.1, scan rate 5 mVs⁻¹.

one polymer monolayer thick) film of polymer **I** and glucose oxidase was electrodeposited by applying a single (2+2)-s pair of square waves. The enzyme was not leached from the ultrathin film when the electrode was rotated at 500 rpm in a buffered glucose solution: The negative branch of the voltammogram was totally absent, as it was in the voltammogram of the electrode on which a film 50 times thicker was deposited (Figure 4).

While the reaction centers of glucose oxidase that have been reduced by glucose cannot be directly electrooxidized on carbon electrodes, oxidized reaction centers of adsorbed soybean peroxidase and of laccase might be directly electroreduced on films comprising small graphite particles. To test for possible catalysis by soybean peroxidase directly adsorbed at the uncoated vitreous carbon electrode, the electrode was

Table 1. Examples of electrodeposited and non-electrodeposited redox polymers.

Polymer	Film deposition	$E_{1/2}^{ox}$ [mV] (solution)	$E_{1/2}^{ox}$ [mV] (film)	Coverage, $\Gamma \times 10^{10}$ mol cm ⁻²	Film
V	yes	-10	20	4.2	stable
VI	no	545	—	—	—
IV	no	550	—	—	—
III	yes	-130	-90	6.2	stable
II	yes	325	340	7.8	stable

soaked in a soybean peroxidase solution (25 mg mL⁻¹) for 2 h, rinsed and its voltammogram was measured in a buffered H₂O₂ solution (2 mM). Comparison of the voltammogram with that of an electrode that was not immersed in the soybean peroxidase solution showed no measurable difference. Furthermore, while H₂O₂ is catalytically electroreduced already at a potential as positive as +0.35 V vs Ag/AgCl on the electrode with the co-electrodeposited film of soybean peroxidase and **I**, electroreduction of H₂O₂ was not observed on the vitreous carbon electrode exposed to the soybean peroxidase solution at potentials positive of -0.08 V vs Ag/AgCl, ruling out the possibility that the reduction of hydrogen peroxide is catalyzed by directly adsorbed soybean peroxidase.

The results show that four conditions must be met for a crosslinking and an electro-deposition of redox polymers based on ligand exchange: first, the film must be electron- or hole-conducting, otherwise only an insulating, necessarily very thin film is deposited; second, the redox centers of the deposited polymer that are based on transition metal complexes must contain in their inner coordination sphere a labile ligand; third, the redox polymer must contain in its backbone a strongly coordinating but yet uncoordinated ligand; fourth, because neighboring chains exchange ligands in the crosslinking process, the surface density of the adsorbed redox polymer must be high, otherwise the fraction of crosslinked polymer will be small.

Experimental Section

[Os(bpy)₂Cl₂] (bpy = 2,2'-bipyridine) was synthesized from K₂OsCl₆ by the procedure of Lay et al.^[26] The syntheses of the redox polymers is shown in Scheme 1, poly(4-vinylimidazole-co-acrylamide) partially complexed with [Os(bpy)₂Cl]⁺/[Os(bpy)₂Cl]²⁺ (**I**),^[27] poly(4-vinylpyridine) partially complexed with [Os(bpy)₂Cl]⁺/[Os(bpy)₂Cl]²⁺ and partially quaternized with 2-bromoethylamine (to increase its solubility in water, **II**),^[25] poly(*N*-vinylimidazole) partially complexed with [Os(4,4'-diamino-2,2'-bipyridine)₂Cl]⁺/[Os(4,4'-diamino-2,2'-bipyridine)₂Cl]²⁺ (**III**),^[28] poly(*N*-vinylimidazole) partially complexed with [Os(4,4'-dimethyl-2,2'-bipyridine)(terpyridine)]²⁺/[Os(4,4'-dimethyl-2,2'-bipyridine)(terpyridine)]³⁺ (**IV**),^[20] poly(*N*-vinylimidazole) partially complexed with [Os(bpy)₂Cl]⁺/[Os(bpy)₂Cl]²⁺ (**V**),^[19] and poly(*N*-vinylimidazole) partially complexed with [Os(bpy)(terpyridine)]²⁺/[Os(bpy)(terpyridine)]³⁺ (**VI**)^[28] were described earlier. Glucose oxidase (GOX, EC 1.1.3.4, Type X-S, from *Aspergillus niger*, 213 units mg⁻¹ of solid) was purchased from Fluka (Fluka Chime AG, Buchs). Horseradish peroxidase (HRP, EC 1.11.1.1, Type VI, 330 units mg⁻¹) and laccase (EC 1.10.3.2, 180 units mg⁻¹) were purchased from Sigma Chemical Co. (St. Louis, MO), and soybean peroxidase (SBP, HP grade, 130 pyrogallol units mg⁻¹) was purchased from Enzymol International, Inc. The phosphate-buffered saline solution (PBS) (pH 7.1, 0.15 M NaCl, 0.02 M phosphate) was freshly prepared using deionized water.

3-mm diameter vitreous carbon electrodes were used. They were polished with alumina, rinsed with deionized water and cycled between -0.4 and +0.8 V in PBS buffer until the featureless voltammograms of sequential cycles were identical. The electrochemical experiments were carried out using a CH Instruments Model 832 electrochemical detector (CH Instruments, Austin, TX). The three-electrode cell had a glassy carbon working electrode, a BAS micro Ag/AgCl reference electrode and a platinum foil counter electrode. The electrodes were placed in a homemade 1.0-mL electrochemical cell. An Analytical Rotator (Pine Instrument Company, Grove City, PA) was used to control mass transport. All reported potentials are referred to the Ag/AgCl (3 M NaCl) reference electrode.

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Formation of a Nonaoxirane from A2E, a Lipofuscin Fluorophore related to Macular Degeneration, and Evidence of Singlet Oxygen Involvement**

Shimon Ben-Shabat, Yasuhiro Itagaki, Steffen Jockusch, Janet R. Sparrow,* Nicholas J. Turro,* and Koji Nakanishi*

The lipofuscin that accumulates in retinal pigment epithelium (RPE) cells may play a role in the deterioration and death of RPE cells which is typical of atrophic age-related macular degeneration (AMD). In human RPE cells, the deposition of this aging pigment is already apparent by age 20,^[1] and while it continues to increase until approximately age 70, thereafter it declines.^[2–4]

The major hydrophobic fluorophores of RPE lipofuscin are the pyridinium bisretinoids A2E (**1**) (Figure 1, top left) and iso-A2E, its 13-Z photo-isomer.^[5–8] A2E is formed by hydrolytic cleavage of A2-PE, a precursor generated from the reaction between two molecules of *all-trans*-retinal and phosphatidylethanolamine (PE).^[9] It has recently been shown that the accumulation of A2E by cultured RPE bestows a sensitivity to light-induced damage.^[10, 11] Specifically, the blue region of the spectrum was found to induce the apoptotic death of A2E-containing cells, with a wavelength dependency that reflected the excitation spectrum of A2E.^[11, 12] The propensity for A2E-laden RPE cells illuminated by blue light to undergo apoptosis is consistent with the known susceptibility of RPE cells to blue light damage in animal models.^[13–15] Moreover, the ability of A2E to serve as an initiator of photodamage may be relevant to studies linking the incidence of advanced atrophic AMD with blue light exposure, particularly in later life.^[16]

To investigate the blue-light-induced modification of A2E, solutions of it in phosphate-buffered saline (PBS) (200 μ M; 200 μ L) containing 0.1 % of DMSO for solubility purposes were irradiated with blue light ((430 $\pm$ 10) nm) delivered from a 150-W tungsten halogen lamp (radiant energy 0.19 mW mm^{–2}). Irradiation for 10 min generated a series of oxidative derivatives, each of which represented the addition

of an oxygen atom at a carbon–carbon double bond (see Figure 3). Irradiation at longer wavelengths where A2E does not absorb gave no reactions. For further structural studies oxidation with *meta*-chloroperoxybenzoic acid (MCPBA) was performed. Purification of the reaction mixture by HPLC yielded **2** as the main component.

FAB (fast atom bombardment) high energy collision-induced dissociation (CID) mass spectra of **2** resulting from the photooxidation and/or MCPBA oxidation showed the same intense *M*⁺ peak at *m/z* 624, and product ions at *m/z* 458 and 488 (Figure 1). Analysis of these ions led to the shown

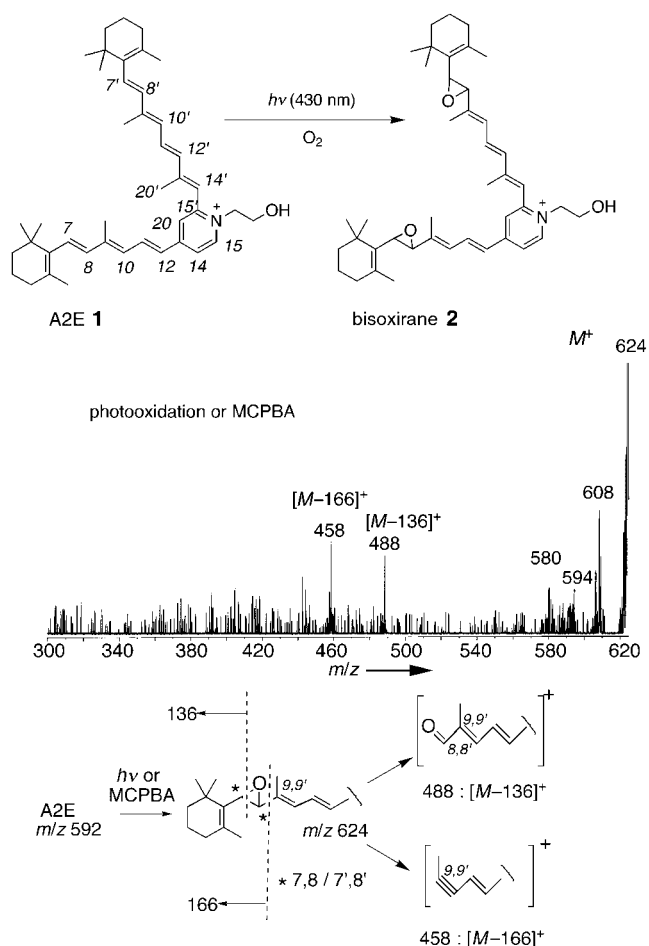


Figure 1. Top: Structures of A2E (**1**) and the bisoxirane **2**. Center: The FAB-CID mass spectra of **2** resulting from photooxidation and from chemical oxidation with MCPBA show the same intense product ions at *m/z* 488 and 458; spectrometer used: JMS HX 110A/110A MS/MS; acceleration voltage 10 kV, collision cell floating 8 kV, collision gas He. Bottom: probable fragment ions.

bisoxirane structure for **2**, a mixture of diastereomers as well as enantiomers, formed by epoxidation of the 7,8 and 7',8' double bonds. Opening of one epoxide ring at the C7/C8–O bond and MS cleavage of the C7/C8–C8/C9 bond gives rise to the fragment *m/z* 488 [*M* – 136]⁺ while cleavage of the C8/C9–C9/C10 bond gives rise to the fragment *m/z* 458 [*M* – 166]⁺ (Figure 1, bottom). Since the charge is localized on the pyridine ring, only product ions containing the pyridinium moiety are observed. Further corroboration for the structural

[*] Prof. J. R. Sparrow
Department of Ophthalmology, Columbia University
New York, NY 10028 (USA)
Fax: (+1) 212-305-9638
E-mail: jrs88@columbia.edu
Prof. N. J. Turro, Dr. S. Jockusch
Department of Chemistry, Columbia University
New York, NY 10027 (USA)
Fax: (+1) 212-932-1289
E-mail: turro@chem.columbia.edu
Prof. K. Nakanishi, Dr. S. Ben-Shabat, Dr. Y. Itagaki
Department of Chemistry, Columbia University
New York, NY 10027 (USA)
Fax: (+1) 212-932-8273
E-mail: kn5@columbia.edu
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assignment ($C_{42}H_{58}O_3N$) of **2** was provided by high-resolution mass spectrometry ($[M]^+$ obs. 624.4420, calc. 624.4417). The UV/Vis spectrum (EtOH) of **2** showed the expected hypsochromic shift relative to the absorption of A2E: $\lambda = 405$, 293 nm (**2**); 434 ($\epsilon = 30\,000$), 335 nm (21 700) (A2E).^[14]

The structure of **2** was corroborated by NMR spectroscopy (Figure 2). In comparison with A2E (Figure 2A), the signals of the protons at C7/8 and C7'/8' were shifted upfield while those of the protons at C10/12 and C10'/12' were unchanged (Figure 2B). ^1H - ^1H COSY and ROESY correlations confirmed the above data and also verified that the pyridinium ring remained unchanged during the oxidation process (Figure 2, bottom).

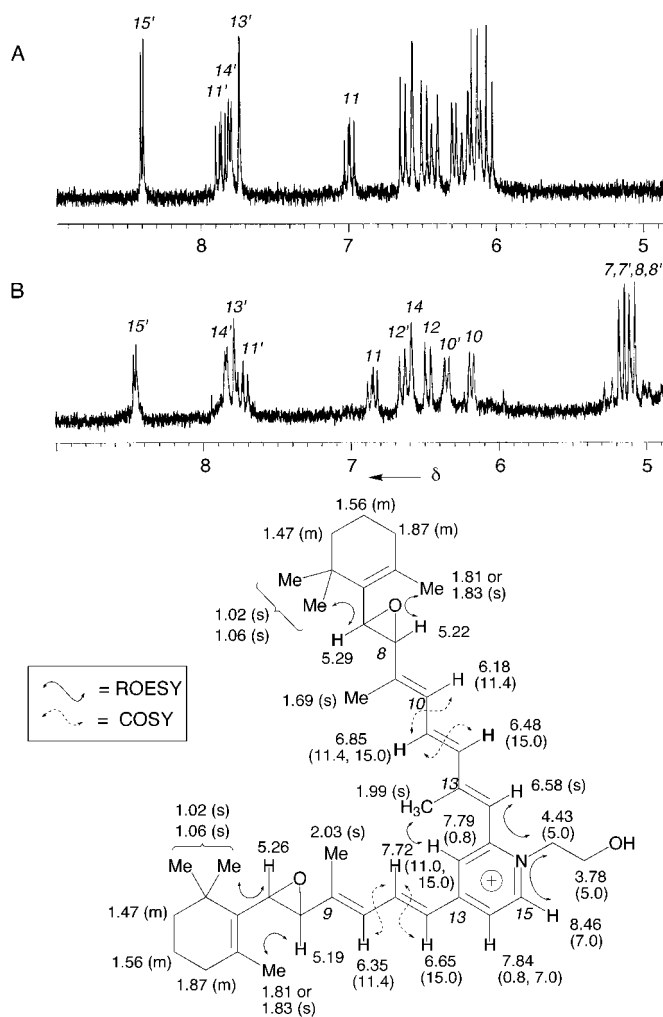


Figure 2. Top: ^1H NMR spectra of A2E (A) and the bisoxirane **2** (B), 400 MHz, CD_3OD . Bottom: assignment of the signals and observed COSY and ROESY peaks.

Subjecting the polyepoxide mixture to APCI (atmospheric pressure chemical ionization) mass spectrometry led to cleavage of the epoxide groups and decomposition of the fragments, giving the pyridine peak at m/z 79 (base peak). Continued irradiation of the polyepoxides led to further photodegradation, showing in all cases the m/z 79 base peak (APCI). The data support the conclusion that the photo-oxidation reaction starts at the 7,8 and 7',8' double bonds and

then occurs at other double bonds. ESI (Figure 3) and FAB mass spectrometry show that epoxidation occurs at all nine double bonds in the hydrocarbon units without modifying the pyridinium ring. The m/z 736 peak and the series of $m/z + 16$ peaks starting from the M^+ peak of A2E demonstrate formation of an unprecedented nonaoxirane of A2E (**3**); no peak other than that of the pyridinium ion (m/z 79) was present below the m/z 592 peak.

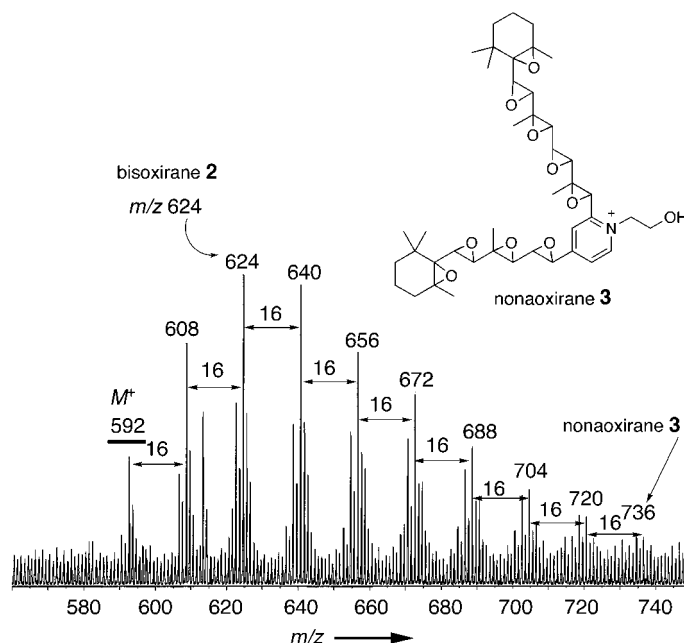


Figure 3. ESI mass spectrum of A2E after illumination with blue light (430 nm; 10 min) to yield **3**. A series of peaks that differ in m/z by 16 show the addition of oxygen atoms. The addition of oxygen occurred at carbon-carbon double bonds (epoxidation) of A2E, the initial oxidations taking place at positions 7,8 and 7',8'. Measured by Micromass ESI-Q-TOF.

It is well known that singlet oxygen is a major intermediate in the photodynamic effect, the combined action of light, dye, and oxygen on a biological substrate.^[17] Furthermore, singlet oxygen is known to add to double bonds giving epoxides.^[18] Thus, to investigate the involvement of singlet oxygen in the epoxidation of A2E, the decrease in A2E levels during irradiation at 430 nm in H_2O and D_2O was determined by HPLC. Quantitative analysis showed two- to threefold greater decrease of A2E in D_2O than in H_2O . Due to the longer lifetime of singlet oxygen in D_2O (68 μs)^[19] compared to H_2O (4.2 μs)^[19] the epoxidation and the decrease in A2E levels should be faster in D_2O than in H_2O . Indeed, a strong isotope effect was observed. The rate of A2E decomposition increased by a factor of ten in CD_3OD ($\tau(^1O_2) = 270 \mu s$ ^[20]) compared to CH_3OH ($\tau(^1O_2) = 9.5 \mu s$ ^[19]) as determined by HPLC analysis.

This large deuterium isotope effect suggests the involvement of singlet oxygen, probably generated by photosensitization with excited states of A2E. Excited states of A2E are efficiently quenched by triplet oxygen present in the solution to produce singlet oxygen. A2E absorbs blue light more efficiently than any of the products. However, despite the fact that the higher epoxides, for example the octaoxirane, do not

absorb blue light (430 nm), epoxidation continues to the nonaoxirane stage. Presumably the remaining A2E acts as a singlet oxygen sensitizer and the singlet oxygen then reacts with the polyoxiranes eventually leading to the unprecedented molecule **3** with nine epoxide rings.

Singlet oxygen can also be generated from the decomposition of aromatic endoperoxides.^[21] The endoperoxide of 1,4-dimethylnaphthalene was selected for our experiments because of its convenient half-life of approximately 5 h at 25 °C, where it decomposes into 1,4-dimethylnaphthalene and singlet oxygen.^[22] Solutions of A2E and the endoperoxide in methanol were stored in the dark for 10 h at room temperature. MS measurements of the reaction mixture revealed epoxidation of A2E and showed a spectrum similar to that of Figure 1.

Chemiluminescence studies confirmed the release of singlet oxygen from the endoperoxide. In CCl₄ it showed a strong chemiluminescence centered at 1270 nm, typical for singlet oxygen phosphorescence.^[23] In the presence of A2E the luminescence intensity was reduced gradually with increasing A2E concentration, suggesting an efficient quenching reaction (Figure 4). The rate constant of the singlet oxygen

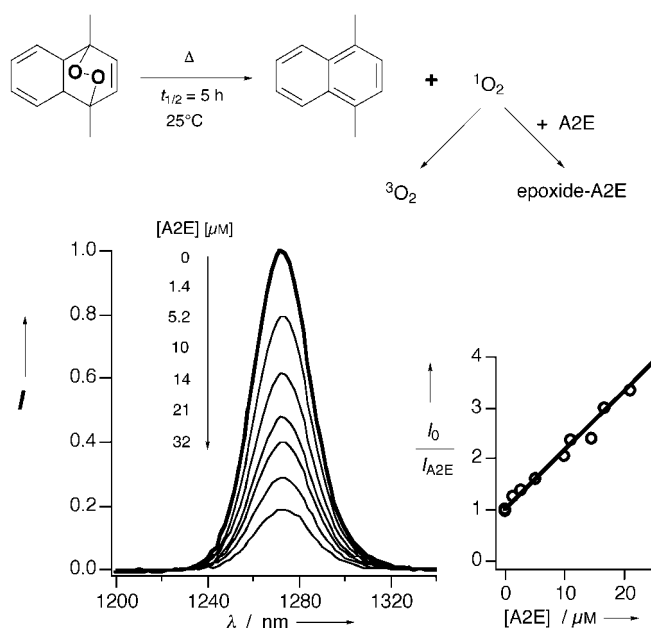


Figure 4. Chemiluminescence spectra (left) of singlet oxygen generated from the endoperoxide of 1,4-dimethylnaphthalene (2.0 mM) in the presence of A2E at different concentrations (0–32 μM) in CCl₄ at 25 °C. Right: the corresponding Stern–Volmer plot to determine the quenching rate constant, where I_0 is the intensity of the chemiluminescence at 1270 nm in the absence of A2E and I_{A2E} is the intensity in the presence of A2E.

quenching was determined by a Stern–Volmer treatment of the luminescence intensities.^[24] The lifetime of singlet oxygen in CCl₄ under experimental conditions (that is at high concentrations of the endoperoxide) is expected to be significantly shorter than in pure CCl₄ (59 ms (photosensitization with 5,10,15,20-tetraphenylporphyrine)).^[19] Therefore, the singlet oxygen lifetime ($\tau(^1\text{O}_2) = 3.4$ ms) was determined by luminescence quenching with 1-methyl-1-cyclohexene

using its known quenching rate constant ($3.6 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$).^[25] This lifetime led to an estimation of the rate constant for the quenching of singlet oxygen by A2E to be $k_{\text{A2E}} \sim 3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$. Irradiation of A2E in CCl₄ with 430-nm light showed a luminescence around 1270 nm (see the Supporting Information), which is typical for the phosphorescence of singlet oxygen.^[23]

In conclusion, it has been shown that A2E undergoes photooxidation during irradiation with blue light, producing epoxide rings initially at positions 7,8 and 7',8'. The deuterium solvent-effect experiments utilizing endoperoxide, phosphorescence, and chemiluminescence quenching studies strongly support the involvement of singlet oxygen. It is proposed that upon irradiation, A2E acts as a sensitizer for generation of singlet oxygen from triplet oxygen present in the solution, and that subsequently the singlet oxygen reacts with A2E to produce epoxides, eventually the nonaoxirane **3**.

Experimental Section

Preparation of bisoxirane **2**: A solution of A2E (1.6 mg, 2.2 μmol) and MCPBA (0.39 mg, 2.2 μmol) in CHCl₃ (4.0 mL) was stirred at room temperature in a sealed vial overnight. The mixture was concentrated in vacuo and purified by reversed phase HPLC (Cosmosil C18, 250 $\times$ 4.6 mm) using acetonitrile in water (0.1% TFA): 85–96% (10 min), 96% (5 min), 96–100% (2 min), 100% (13 min); monitored at 430 nm.

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Reversible Binding of C₆₀ to an Anthracene Bearing a Dendritic Poly(amidoamine) Substituent to give a Water-Soluble Fullerodendrimer**

Yutaka Takaguchi,* Tomoyuki Tajima, Kazuchika Ohta, Jiro Motoyoshiya, Hiromu Aoyama, Takatsugu Wakahara, Takeshi Akasaka,* Mamoru Fujitsuka, and Osamu Ito*

Fullerene-based compounds are attracting much interest in the fields of structural and synthetic organic chemistry.^[1–3] In particular, there is an increasing focus on developing applications for fullerene-functionalized dendrimers (fullerodendrimers), because of a variety of interesting features in supramolecular chemistry and materials.^[1,2] Although a number of synthetic techniques have been devised, [4+2] cycloaddition proved to be one of the most expeditious methods for selective functionalization of [60]fullerene at the 6,6-ring junctions.^[4] Several such reactions of C₆₀ with

anthracenes have been described.^[5–7] However, the formation of fullerodendrimers by a Diels–Alder reaction of C₆₀ with anthracene derivatives has never been reported. Recently, we described the synthesis, characterization, and photodimerization of a poly(amidoamine) dendron with an anthracene moiety at the focal point.^[8] During our studies on the reactivity of this anthracene bearing a dendritic substituent, we found that it underwent reversible Diels–Alder reaction with C₆₀. Although a few examples of fullerodendrimers with amide dendrons have been reported, much less is known about the chemistry of poly(amidoamine) dendrimer grafted to C₆₀.^[9] Here we describe the synthesis and characterization of a poly(amidoamine) dendron with C₆₀ at the focal point. This fullerodendrimer also represents a new class of water-soluble fullerenes and acts as photosensitizer to generate singlet oxygen in water. To our knowledge, the only fullerodendrimer with reversible formation of bonds between C₆₀ and the dendrimer is an iridium complex reported by Catalano et al.^[10]

A mixture of C₆₀ and dendron **1**^[8] (1 equiv) in *o*-dichlorobenzene was irradiated with a high-pressure mercury lamp ($\lambda > 300$ nm) at room temperature under a nitrogen atmosphere for 1 h. The initial purple color of the solution became red as the reaction proceeded. After evaporation under reduced pressure below 60 °C, the products were separated by HPLC (LC 918, Japan Analytical Industry, Co. Ltd.) on gel-permeation columns (Jaigel 2H+1H) with chloroform as eluent to give the fullerodendrimer **2** as a brown oil in 21 % yield (Scheme 1). Notably, **2** is readily soluble in methanol, and hence unreacted C₆₀ was easily removed by filtration after the reaction. Fullerodendrimer **2** remained stable for several weeks when stored at –10 °C. The addition reaction was also conducted by heating at 45 °C for 4 d in *o*-dichlorobenzene in the dark to give **2** in 12 % yield. When fewer equivalents of anthracenyl dendron **1** were used, the

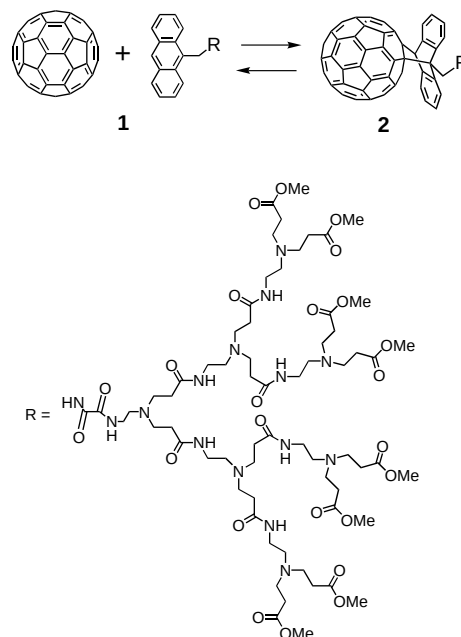
[*] Dr. Y. Takaguchi, T. Tajima, Prof. Dr. K. Ohta, Prof. Dr. J. Motoyoshiya, Prof. Dr. H. Aoyama
 Faculty of Textile Science & Technology
 Shinshu University
 Ueda, Nagano 386-8567 (Japan)
 Fax: (+81)268-21-5391
 E-mail: ytakagu@giptc.shinshu-u.ac.jp

Prof. Dr. T. Akasaka
 Center for Tsukuba Advanced Research Alliance
 University of Tsukuba
 Tsukuba, Ibaraki 305-8577 (Japan)
 Fax: (+81)298-53-6409
 E-mail: akasaka@tara.tsukuba.ac.jp

Prof. Dr. O. Ito, Dr. M. Fujitsuka
 Institute of Multidisciplinary Research for Advanced Materials
 Tohoku University
 Sendai, Miyagi 980-8577 (Japan)
 Fax: (+81)22-217-5608
 E-mail: ito@tagen.tohoku.ac.jp

Dr. T. Wakahara
 Graduate School of Science and Technology
 Niigata University
 Niigata 950-2181 (Japan)

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Scheme 1. Reversible Diels–Alder reaction of C₆₀ and **1**.

equilibrium shifted towards the starting materials, and product yields were lower.

The structure of **2** was confirmed by ^1H and ^{13}C NMR and UV/Vis spectroscopy, and laser desorption/ionization time-of-flight (LD-TOF) mass spectrometry.^[11] The ^{13}C NMR spectrum of **2** shows 36 signals in the sp^2 region, which indicate that the product has a C_s symmetry and that cycloaddition occurred at the 6,6-ring junction, as for anthracene adducts of C_{60} reported so far.^[5–7] The signals of **2** at $\delta = 59.0$, 65.8, 74.9, and 75.8 are reasonably assigned to the bridging sp^3 carbon atoms. The UV/Vis spectrum of **2** in toluene exhibited absorptions at 434 and 702 nm; the former is typical of a 1:1 adduct at the 6,6-ring junction.^[6] The LD-TOF mass spectrum of **2** in the negative-ion mode (Figure 1) showed a molecular ion peak at $m/z = 2414.22$ ($\text{C}_{141}\text{H}_{127}\text{N}_{15}\text{O}_{24}$ requires $m/z = 2414.62$). As was observed for [4+2] cycloadducts of C_{60} ,^[5a] the fullerodendrimer **2** has a more negative reduction potential ($E_{\text{red}}^1 = -1.25$ V) than C_{60} ($E_{\text{red}}^1 = -1.12$ V).

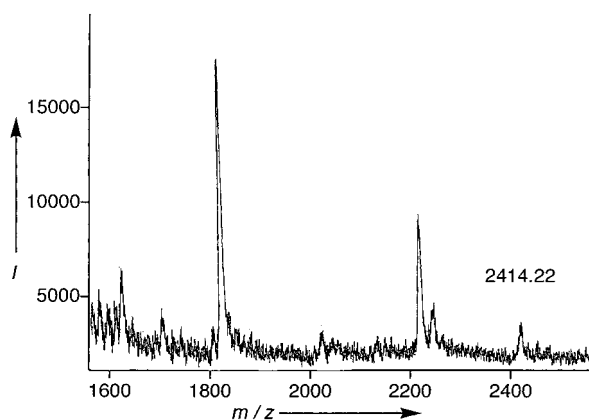


Figure 1. Negative-ion LD-TOF mass spectrum of fullerodendrimer **2**. I = intensity.

It is well known that adducts of C_{60} and anthracene undergo retro-Diels–Alder reactions. To clarify the utility of anthracenyl dendron **1** as a fullerene reservoir, we investigated the possibility of the retroreaction. Heating **2** in methanol at 45°C for 12 h gave the component molecules C_{60} and dendron **1** in 89 and 87% yield, respectively. Thus, the reaction is reversible, and there is an equilibrium between bond-forming and dissociation reactions.

It is notable that the fullerodendrimer **2** is readily soluble in acidic water: Saturated concentrations of **2** in H_2O are 20.5 (pH 1.50), 2.19 (pH 5.46), and 0.038 mM (pH 6.51). We investigated photophysical and photochemical properties of **2** in water. The transient spectra observed by laser excitation of **2** in deaerated water are shown in Figure 2A. The absorption peak at 700 nm is assigned to the absorption of the triplet excited state of **2**, because this peak is in good agreement with the triplet–triplet absorption of C_{60} adducts.^[12] From the decay at 700 nm, the triplet lifetime was evaluated to be 56 μs . On addition of O_2 , the decay rate increased (Figure 2B), and this indicates that energy transfer from the triplet state of **2** to O_2 takes place to produce singlet oxygen. From the decay in O_2 -saturated water, the rate constant for energy transfer from the triplet state of **2** to O_2 was found to be

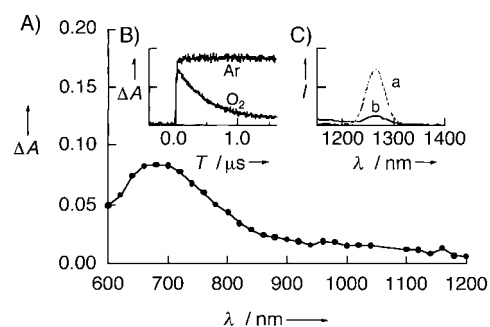


Figure 2. A) Transient absorption spectra observed by nanosecond laser (532 nm) excitation of **2** in deaerated water. B) Time profiles at 700 nm in the absence and presence of O_2 . C) Emission spectra in the NIR region; a) C_{60} in toluene; b) **2** in D_2O . A = absorbance.

$1.3 \times 10^9 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$. The formation of singlet oxygen was confirmed by the observation of its emission at 1280 nm in D_2O (Figure 2C), from which the quantum yield of singlet oxygen was estimated to be 0.45 after correcting the low O_2 concentration in D_2O by comparison with a standard solution in toluene.^[13]

We have demonstrated the first example of reversible formation of a fullerodendrimer in a Diels–Alder reaction. This system is useful for the synthesis of fullerodendrimers and as a fullerene reservoir. The use of the photoexcited state of this water-soluble fullerodendrimer as a singlet-oxygen sensitizer was also investigated. Potentially important practical applications of this fullerodendrimer are as a removable solubilizing group for fullerenes and as a biologically active agent that releases C_{60} intracellularly. Further work is in progress to explore the applications and advantages of the reversible formation of fullerodendrimers.

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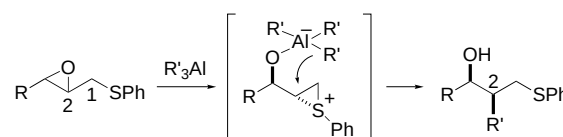
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 [11] ¹H NMR (400 MHz, [D₈]toluene): δ = 2.17–2.63 (m, 24H), 2.32–2.83 (m, 46H), 3.29–3.40 (m, 14H), 3.43 (d, J = 1.6 Hz, 2H), 3.48 (s, 24H), 3.48–3.57 (m, 8H), 6.91–7.95 (m, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 32.7, 33.8, 34.0, 36.1, 37.1, 37.5, 49.2, 49.9, 51.65, 51.67, 52.2, 52.6, 52.9, 55.0, 59.0, 65.9, 74.7, 75.6, 123.7, 125.2, 126.8, 127.8, 128.4, 129.2, 136.5, 137.3, 138.8, 140.1, 141.39, 141.4, 141.6, 141.9, 142.0, 142.1, 142.59, 142.60, 142.62, 142.64, 142.9, 144.5, 144.6, 145.0, 145.18, 145.22, 145.33, 145.37, 145.40, 145.9, 146.1, 146.2, 146.4, 146.5, 152.4, 155.8, 159.52, 159.59, 172.2, 172.4, 173.1; UV/Vis (toluene): λ_{max} (ε) = 434.4 (1500), 702.0 nm (153); LD-TOF MS: C₁₄₁H₁₂₇N₁₅O₂₄: m/z calcd: 2414.62 [M]⁺; found: 2414.22.
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Stereospecific Interconversion between *cis* and *trans* 2,3-Epoxy sulfides**

Atsushi Hirai, Terumichi Tonooka, Kofumi Wakatsuki, Keiji Tanino, and Masaaki Miyashita*

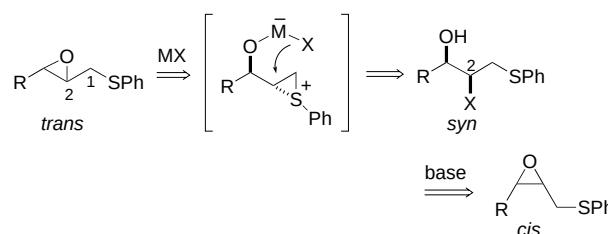
Ring-opening reactions of epoxides with nucleophiles provide a useful method for the stereoselective synthesis of organic compounds.^[1] In this type of transformation, the relative stereochemistry of the products reflects that of the parent epoxides, which are usually prepared in the *cis* or *trans* forms from the corresponding *Z* or *E* olefins, respectively.^[2] In this connection, however, the interconversion between the *cis* and *trans* epoxides, which contrasts with the configurational isomerization of olefins that is possible by some methods, has not been reported.^[3]

Recently, Saigo and co-workers and our group have independently reported that the reaction of a 1-(phenylthio)-2,3-epoxyalkane with an organoaluminum reagent resulted in regio- and stereoselective substitution at C2, with double inversion of configuration (Scheme 1).^[4, 5]



Scheme 1. Proposed reaction mechanism of the alkyl substitution reaction with double inversion of the configuration.

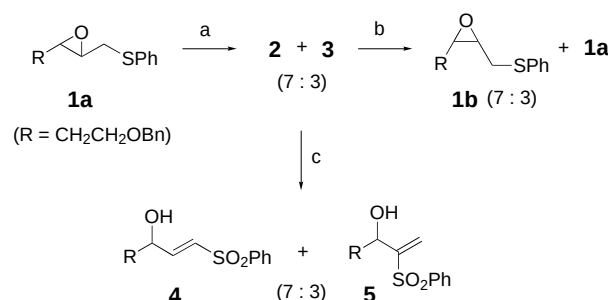
The characteristic stereochemical results, which can be rationalized by assuming an episulfonium ion intermediate, have led us to design a new method for the interconversion between *cis* and *trans* epoxides (Scheme 2): the reaction of a



Scheme 2. Interconversion between *cis* and *trans* epoxides (X = halogen).

trans 2,3-epoxy sulfide with a metal halide should afford a *syn* 2-halo-3-alkanol with double inversion of configuration at C2. On treatment with a base, the resulting *syn* halohydrin would undergo an intramolecular S_N2 reaction at C2 to yield the corresponding *cis* 2,3-epoxy sulfide. The application of a similar procedure to a simple *trans* epoxide merely results in the recovery of the same *trans* epoxide via an *anti* halohydrin intermediate.^[6]

First, *trans*-5-benzyloxy-2,3-epoxy-1-phenylthiopentane (**1a**) was treated with MgBr₂·OEt₂^[7] at 0 °C in toluene, and an inseparable 7:3 mixture of bromohydrins **2** and **3** was obtained (Schemes 3 and 4). The crude product was treated with potassium carbonate in methanol^[8] to give a 7:3 mixture of *cis*-epoxide **1b** and *trans*-epoxide **1a**. On the other hand, treatment of the crude bromohydrins **2** and **3** with



Scheme 3. Reagents and conditions: a) MgBr₂·OEt₂, toluene, 0 °C; b) K₂CO₃, MeOH; c) 1. MCPBA, 2. DBU. MCPBA = *meta*-chloroperoxybenzoic acid; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

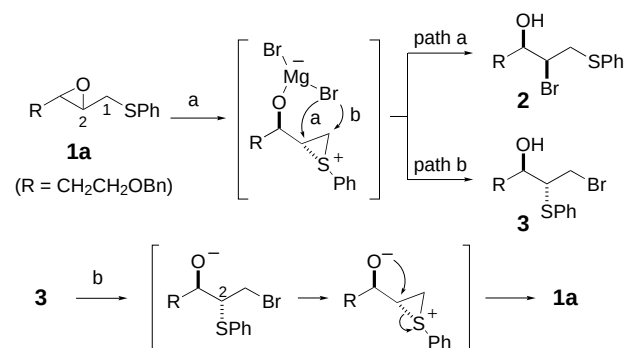
[*] Prof. Dr. M. Miyashita, Dr. A. Hirai, T. Tonooka, K. Wakatsuki, Dr. K. Tanino
 Division of Chemistry, Graduate School of Science
 Hokkaido University
 Sapporo 060-0810 (Japan)
 Fax: (+81)11-706-4920
 E-mail: miyashita@sci.hokudai.ac.jp

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*m*CPBA followed by DBU afforded a 7:3 mixture of unsaturated sulfones **4** and **5** in almost quantitative yield.

These results can be rationalized by a reaction mechanism that involves an episulfonium ion species as a common intermediate of bromohydrins **2** and **3** (Scheme 4).^[9] Since the reaction of **3** with potassium carbonate can not yield an



Scheme 4. Reagents and conditions: a) MgBr₂·OEt₂, toluene, –20 °C; b) K₂CO₃, MeOH.

epoxide directly, migration of the phenylthio group at C2 to C1 via an episulfonium ion intermediate would account for the formation of epoxide **1a**. In the course of the studies described above, bromohydrin **3** was found to undergo spontaneous isomerization to **2**, even after aqueous work-up.^[10] Thus, the ratio of **2** and **3** was changed from 7:3 to 9:1 after standing in CDCl₃ at room temperature overnight. The isomerization reaction might proceed through an episulfonium ion intermediate, though the origin of the lower stability of **3** is not clear at present. After further investigation, we found that **3** can be transformed almost completely into **2** by heating the crude bromohydrin at 60 °C in toluene for 3 d. Treatment of the resulting bromohydrin **2** with K₂CO₃ in isopropyl alcohol at room temperature^[11] afforded the desired *cis* epoxide **1b** highly stereoselectively (97:3) in 95 % yield from **1a**.

The excellent preliminary results prompted us to examine a variety of *trans* epoxysulfides under these conditions. The results are summarized in Table 1. Epoxysulfide **6**, which has no functional group on its side chain, was converted into the

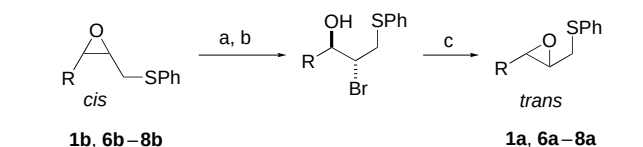
Table 1. Conversion of *trans* epoxides into the corresponding *cis* epoxides.^[a]

Entry	Conditions	R	Yield [%] ^[b] <i>cis:trans</i>
1	–20 °C, 2 h	CH ₃ CH ₂ CH ₂ (6)	99 99:1
2	–20 °C, 2 h	BnOCH ₂ (7)	99 98:2
3	–20 °C, 2 h	(<i>i</i> Pr) ₃ SiOCH ₂ (8)	94 98:2
4 ^[c]	–20 – –10 °C, 8 h	AdCO ₂ CH ₂ CH ₂ CH ₂ (9)	97 98:2
5 ^[c]	–20 – –10 °C, 22 h	PhtNCH ₂ CH ₂ CH ₂ (10)	95 99:1

[a] Reagents and conditions: a) MgBr₂·OEt₂, toluene, see column 2; b) toluene, 60 °C, 3 d; c) K₂CO₃, *i*PrOH, room temperature, 1 day. [b] Yield over two steps. [c] Ad = 1-adamantyl, Pht = *o*-C₆H₄(CO)₂.

corresponding *cis* epoxide with extremely high stereoselectivity (Table 1, entry 1). Similarly, epoxysulfides that bear oxygen functional groups or a nitrogen functional group also gave excellent results (Table 1, entries 2–5). Conversion of the *cis* epoxides into the corresponding *trans* epoxides was examined by using a similar procedure (Table 2). In these cases, the bromohydrin intermediates were slightly labile in the presence of MgBr₂·OEt₂, and a considerable amount of ketone was formed by means of a 1,2-hydride shift. Fortunately, however, performing the first step at –20 °C effectively reduced the side reaction, and the desired *trans* epoxides were obtained in excellent yields and with high stereoselectivity.

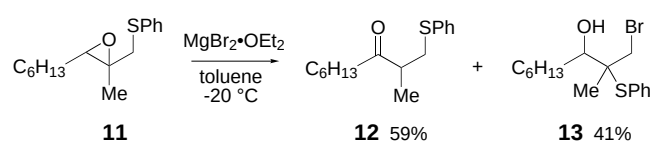
Table 2. Conversion of *cis* epoxides into the corresponding *trans* epoxides.^[a]



Entry	Conditions	R	Yield [%] ^[b] <i>cis:trans</i>
1	–20 °C, 0.5 h	CH ₃ CH ₂ CH ₂ (6)	94 3:97
2	–20 °C, 0.5 h	BnOCH ₂ (7)	98 5:95
3	–20 °C, 3 h	(<i>i</i> Pr) ₃ SiOCH ₂ (8)	83 5:95
4	–20 °C, 2 h	BnOCH ₂ CH ₂ (1)	96 2:98

[a] Reagents and conditions: a) MgBr₂·OEt₂, toluene, see column 2; b) toluene, 60 °C, 3 d; c) K₂CO₃, *i*PrOH, room temperature, 1 day. [b] Yield over two steps.

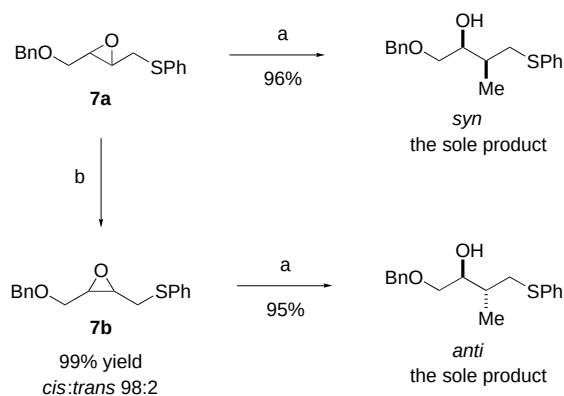
To determine further the scope and limitation of the present transformations, a reaction with trisubstituted epoxysulfide **11** was examined (Scheme 5). However, treatment of **11** with MgBr₂·OEt₂ resulted in the formation of ketone **12** as the major product along with bromohydrin **13**. In this case, the introduction of a bromine atom at C2 might be impeded as a result of increased steric hindrance.



Scheme 5. The reaction of a trisubstituted epoxysulfide.

In conclusion, a novel method for the interconversion of *cis* and *trans* epoxides was developed. To the best of our knowledge, this is the first protocol of this type of transformation. Although the present method can be applied only to disubstituted 1-phenylthio-2,3-epoxyalkanes, these compounds have been demonstrated to be potential intermediates for stereoselective transformations, for example, see Scheme 6.^[4, 5] Application of this method in the synthesis of natural products is underway in our laboratory.

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Scheme 6. Reagents and conditions: a) Me_3Al (3 equiv), CH_2Cl_2 , -30°C ; b) our method.

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Asymmetric Epoxidation of Allyl Alcohol on Organic–Inorganic Hybrid Chiral Catalysts Grafted onto the Surface of Silica and in the Mesopores of MCM-41**

Song Xiang, Yiliang Zhang, Qin Xin, and Can Li*

Asymmetric epoxidation of allylic alcohols is an important reaction in synthetic organic chemistry.^[1] Sharpless and Katsuki^[2] have provided an excellent homogeneous catalytic

system for this reaction which consists of titanium tetraisopropoxide and a chiral dialkyl tartrate. Heterogeneous systems have tremendous advantages over homogeneous catalytic systems.^[3] One of the most attractive advantages is the easy separation of the product from the catalyst without tedious experimental work-up.

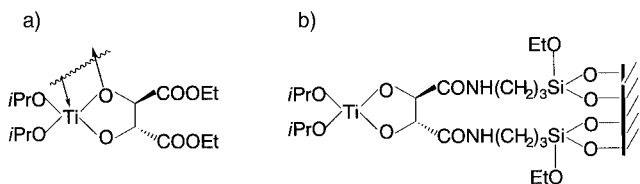
Different approaches have been used in the preparation of heterogeneous Sharpless-type catalytic systems for the asymmetric epoxidation of allylic alcohols. An early attempt to develop a polymer-supported system employed a single tartrate ester unit bound to a polystyrene resin;^[4a] in this case, the chiral induction was only modest (ca. 50–60% *ee*). Choudary et al.^[4b] reported the asymmetric epoxidation of allylic alcohols with a heterogeneous titanium-pillared montmorillonite catalyst in the presence of chiral tartrate ester. However, the preparation of the solids seems to be difficult to reproduce.^[5] Hormi and co-workers^[4c, 4d] synthesized insoluble branched/crosslinked poly(tartrate ester)s and investigated their use as optically active ligands in the heterogeneous asymmetric epoxidation of allylic alcohols with titanium tetraisopropoxide and *tert*-butyl hydroperoxide. These gel-type polymeric ligands swell during the catalytic reaction. Basset and co-workers^[4e] reported silica-supported tantalum catalysts for the enantioselective epoxidation of allylic alcohols in the presence of chiral tartrate derivatives. Their result is comparable to that obtained in the homogeneous Sharpless reaction. However, the organometallic tantalum compound used in the synthesis is not easy to prepare.^[6]

The preparation of organic–inorganic hybrid materials is of growing interest.^[7, 8] In contrast to organic polymers, organic–inorganic hybrid materials do not swell or dissolve in organic solvents, and have many advantages over most organic polymers because of their superior mechanical and thermal stabilities. Moreover, any leaching could be avoided as the organic moieties are covalently attached to the inorganic supports. For hybrid materials, the design and synthesis of chiral catalytic materials^[8] with high enantioselectivities are especially attractive.^[8c–e] Highly efficient and enantioselective transition metal complexes have been reported in the literature. The design and synthesis of chiral hybrids with activity and enantioselectivity similar to that of homogeneous catalysts remain a challenge. Few reports have appeared on the synthesis of organic–inorganic hybrid chiral materials and on their use as heterogeneous catalysts in enantioselective reactions.^[8c–e] We report herein the synthesis of organic–inorganic hybrid chiral materials by grafting a chiral tartaric acid derivative onto the surface of silica and in the mesopores of MCM-41 material (Scheme 1b), and provide the first example of their successful application in the heterogeneous asymmetric epoxidation of allyl alcohol. The catalytic systems resulted in enantiomer excesses up to 80%, which is as good as the homogeneous Sharpless system (Scheme 1a).

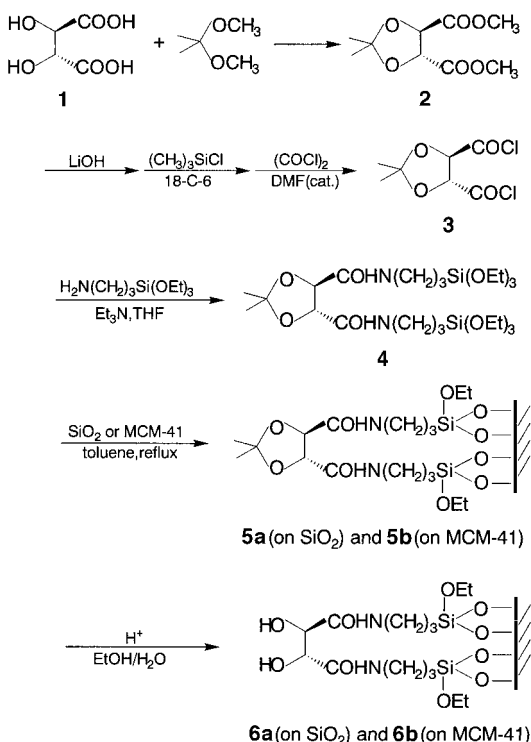
The chiral tartaric derivative was grafted onto inorganic supports in several steps, as outlined in Scheme 2. Tartaric acid (**1**) was converted into the protected tartaric acid dichloride **3**. Treatment of **3** with 3-aminopropyltriethoxysilane gave **4**, which was grafted onto SiO_2 and MCM-41 to afford **5a** and **5b**, respectively. Selective cleavage of the isopropylidene acetal removed the protecting groups and

[*] Prof. Dr. C. Li, S. Xiang, Y. Zhang, Prof. Q. Xin
State Key Laboratory of Catalysis
Dalian Institute of Chemical Physics, Chinese Academy of Sciences
Dalian, 116023 (China)
Fax: (+86) 411-4694447
E-mail: canli@dicp.ac.cn

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Scheme 1. a) Homogeneous chiral catalyst for the asymmetric epoxidation of allylic alcohols, proposed by Sharpless and Katsuki,^[2] which consists of $\text{Ti}(\text{O}i\text{Pr})_4$ and a chiral tartaric derivative (only half of the dimer is shown); b) heterogeneous chiral catalyst, prepared from organic-inorganic hybrid chiral material grafted onto the surface of silica and in the mesopores of MCM-41.



Scheme 2. The synthesis of organic-inorganic hybrid chiral materials on the surface of silica and in the mesopores of MCM-41.

gave the desired **6a** and **6b**, respectively. Although the selective cleavage of the isopropylidene acetal under homogeneous conditions is known, the selective removal of the protecting group grafted onto insoluble inorganic supports has not been reported. In our system, besides the protecting group, the tartaramide and the inorganic Si-O-Si bond can also be hydrolyzed under acidic conditions. The challenge is to selectively hydrolyze the protecting group, while keeping the tartaramide and inorganic Si-O-Si bond intact. If the conditions are too severe, the hybrid material may decompose. It was reported that the protecting group can be removed selectively when the substrate is dissolved and stirred in 90 % acetic acid at room temperature for about 40 h.^[9] Surprisingly, the cleavage of the isopropylidene acetal grafted onto inorganic supports required rather severe conditions and long reaction times. We found that the protecting group could not be removed even when the solid was stirred in 90 % acetic acid at 40 °C for 4 d. Neither could it be removed when the solid was stirred at 40 °C for 4 d in 95 % ethyl alcohol that had

been acidified to pH 4 with concentrated hydrochloric acid. When the pH value was decreased to 3 or below and the hydrolysis was carried out at 40 °C for 4 d, the protecting group could be removed.

The selective removal of the protecting group was confirmed by means of FT-IR and ^{13}C CP/MAS NMR spectroscopy (CP/MAS = cross polarization/magic-angle spinning). IR spectra of the hybrid materials were recorded before and after hydrolysis. The peak at 2889 cm^{-1} , associated with the protecting group, disappeared after hydrolysis, and the characteristic peak at 1666 cm^{-1} for the -CONH- stretching vibration still remained, which indicates the presence of the tartaramide. The ^{13}C NMR spectrum provided more direct evidence for the selective hydrolysis of the protecting group: the signal at $\delta = 113$, assigned to the quaternary carbon atom of the protecting group, remained unchanged when the hydrolysis was performed at $\text{pH} \geq 4$, but disappeared after the hydrolysis at $\text{pH} \leq 3$. Furthermore, the signal associated with the carbon atom attached to the protected hydroxy group shifted from $\delta = 78.3$ to 70.2 as a result of the removal of the protecting group (Figure 1).

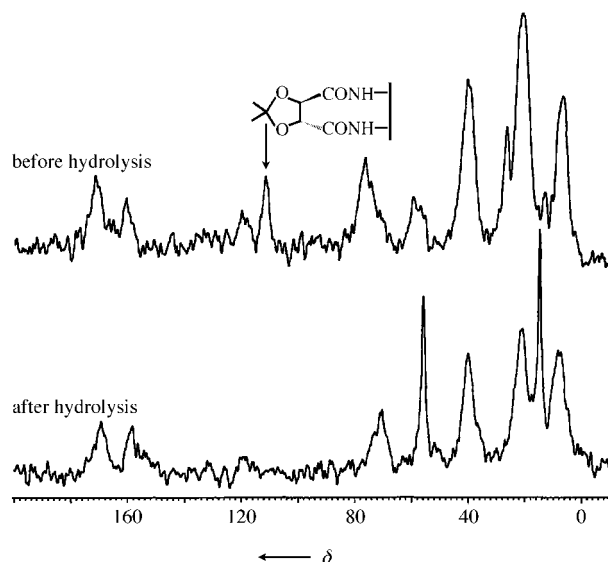
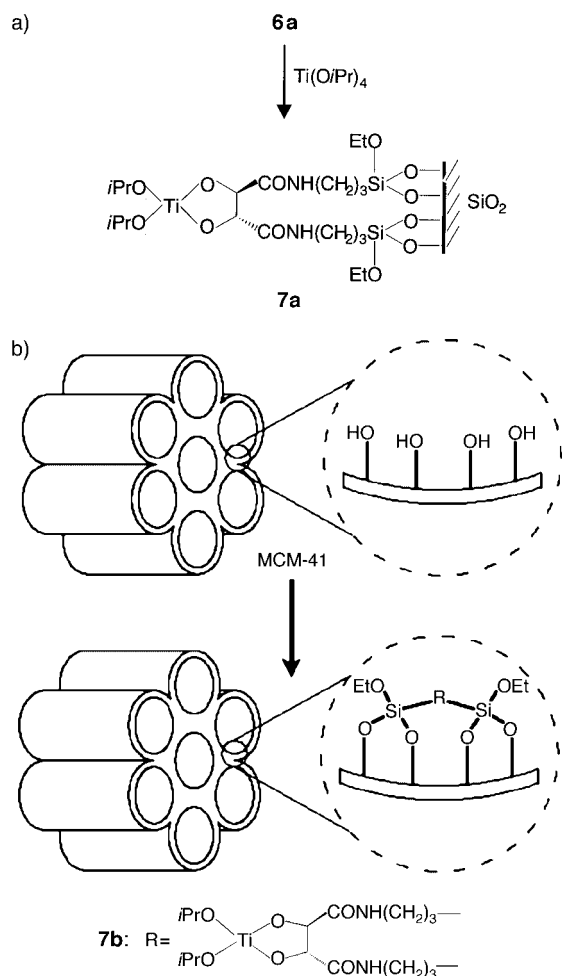


Figure 1. The ^{13}C CP/MAS NMR (400 MHz) of organic-inorganic hybrid chiral materials before and after hydrolysis.

Two kinds of organic-inorganic hybrid chiral materials that contain free hydroxy groups were obtained: on silica (**6a**) and in the mesopores of MCM-41 material (**6b**). The amount of tartaric acid derivative grafted onto the inorganic supports is about 0.5 mmol g^{-1} for **6a** and 0.6 mmol g^{-1} for **6b**, as estimated from elemental analysis data, taking into account mass % carbon and nitrogen.

The chiral catalysts **7a** and **7b** were synthesized directly by the reaction of titanium tetraisopropoxide with the organic-inorganic hybrid chiral materials **6a** and **6b**, respectively (Scheme 3). The synthetic catalysts were formed in situ and tested in the enantioselective epoxidation of allyl alcohol, and the results are presented in Table 1. The activity and enantioselectivity (Table 1, entry 2) are as good as those obtained from the homogeneous Sharpless reaction (Table 1,



Scheme 3. a) Heterogeneous chiral catalyst **7a**, synthesized in situ from **6a**. b) Heterogeneous chiral catalyst **7b**, synthesized in situ from **6b**.

Table 1. Asymmetric epoxidation of allyl alcohol on organic–inorganic hybrid chiral catalysts grafted onto the surface of silica and in the mesopores of MCM-41.

Entry	Catalyst ^[a]	Titanium/substrate ^[b]	Conversion ^[c]	TON	ee [%] ^[c,d]
1	TiP/DET ^[f]	5 %	76 %	15	83
2	7a	2 %	29 %	14	86
3	7b	2 %	22 %	11	84
4	7a	4 %	49 %	12	78
5	7b	4 %	43 %	10	80

[a] See Scheme 3. [b] Molar ratio. [c] Determined after reaction for 48 h at 0 °C by GC with *n*-nonane as internal standard. [d] Determined by means of GC on a chiral β -cyclodextrin column. [f] Ti(OiPr)₄ + L-diethyl tartrate.

entry 1). When the titanium/substrate ratio is increased from 2 to 4 %, the conversion is almost doubled. The increase in conversion is nearly proportional to the amount of titanium used in the epoxidation. The turnover number (TON) is nearly unchanged (Table 1, entry 4), which indicates that the activity and enantioselectivity may result from the monomeric titanium species complexed with the hybrid chiral material.

Chiral tartaric derivative grafted onto mesoporous MCM-41 shows similar results. However, the activity is lower than that of the catalyst grafted onto silica (Table 1, entry 3). This is probably a result of the slower diffusion of the substrate and the product in the mesopores of MCM-41. When the titanium/

substrate ratio is increased from 2 to 4 %, similar results are obtained. Again, the turnover number and the enantiomeric excess are nearly unchanged (Table 1, entry 5). This result indicates that all the titanium species are grafted onto the surface of silica or into the mesopores of MCM-41 in the form of a Sharpless-like complex. From Table 1, it is clear that the heterogeneous catalysts, synthesized from the monomeric titanium species complexed with the hybrid chiral material, show activity and enantioselectivity resembling that of the Sharpless catalyst. The result is in good agreement with our conceptual approach (Scheme 1): the environment surrounding the immobilized species is analogous to that of the homogeneous complex.

In summary, organic–inorganic hybrid chiral materials are synthesized by grafting a chiral tartaric acid derivative onto the surface of silica and in the mesopores of MCM-41, and the synthetic catalysts show enantioselectivities up to 80 % *ee* for the asymmetric epoxidation of allyl alcohol. This is the first example of the application of hybrid chiral materials in heterogeneous asymmetric epoxidation of allyl alcohol. For the chiral hybrids, the environment surrounding the immobilized species is analogous to that of homogeneous chiral complexes. The performance of the heterogeneous catalyst is also similar to the homogeneous Sharpless reaction. Our method could be a general approach to the synthesis of chiral heterogeneous catalysts. A further advantage of the system is that the product can be separated easily from the catalyst by simple filtration.

Experimental Section

2: Synthesized from L-tartaric acid (**1**) according to a literature procedure^[10]. $[\alpha]_D^{25} = -53.8^\circ$ (neat); lit. $[\alpha]_D^{20} = -54^\circ$ (neat).^[11] IR: $\tilde{\nu} = 2994, 2957, 1759, 1439, 1385, 1214, 1113, 859 \text{ cm}^{-1}$; $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 4.8$ (s, 2H; OCH), 3.8 (s, 6H; OCH₃), 1.5 (s, 6H; C(CH₃)₂).

3: Synthesized according to the procedure of Choi et al.^[12] as a light yellow solid (b.p. 52–54 °C/2 mmHg, [lit.]: 51–55 °C/2 mmHg).

4: 3-Aminopropyltriethoxysilane was treated with **3** in dry THF in the presence of Et₃N to afford **4** as a light yellow, viscous oil. IR: $\tilde{\nu} = 3320, 2973, 1672, 1531, 1443, 1385, 1078, 958, 782 \text{ cm}^{-1}$.

5a/5b: L-Tartaramide **4** was grafted onto MCM-41 material (3 g, S_{BET} : 747 m² g⁻¹, pore size: 33.6 Å) and silica (3 g, S_{BET} : 375 m² g⁻¹) to form **5a** and **5b**, respectively, according to a literature procedure.^[13] IR: $\tilde{\nu} = 2994, 2940, 2889, 1666, 1523, 1446, 1390, 804 \text{ cm}^{-1}$; $^{13}\text{C CP/MAS NMR}$ (400 MHz): $\delta = 172.1, 113.0, 78.3, 61.8, 43.0, 23.9, 9.9$.

6a or 6b: The white solid **5a or 5b** (3 g) was hydrolyzed at 40 °C for 4 days in 95 % ethyl alcohol (20 mL) that had been acidified to pH 3 with hydrochloric acid. IR: $\tilde{\nu} = 2940, 1666, 1523, 1446, 1390, 804 \text{ cm}^{-1}$; $^{13}\text{C CP/MAS NMR}$ (400 MHz): $\delta = 169.2, 70.2, 55.8, 39.9, 20.8, 14.8, 8.4$; elemental analysis: **6a:** C 8.56 %, H 1.58 %, N 1.55 %; **6b:** C 11.16 %, H 2.10 %, N 1.95 %.

Epoxidation: Titanium tetrakisopropoxide, the hybrid chiral material **6a or 6b** (or L-(+)-diethyl tartrate; 1.5 equiv relative to titanium), and dry CH_2Cl_2 (20 mL) were added to a 50-mL Schlenk-type flask under an argon atmosphere. The mixture was cooled to 0 °C and stirred for 1 h. Allyl alcohol (10 mmol) and *n*-nonane (internal standard) were added. *tert*-Butyl hydroperoxide (20 mmol) was added dropwise with stirring. The mixture was stirred for 48 h at 0 °C. The reaction was stopped by removing the catalyst from the solution by filtration. Conversions, yields, and *ee* values were determined by means of gas chromatography on a chiral β -cyclodextrin column.

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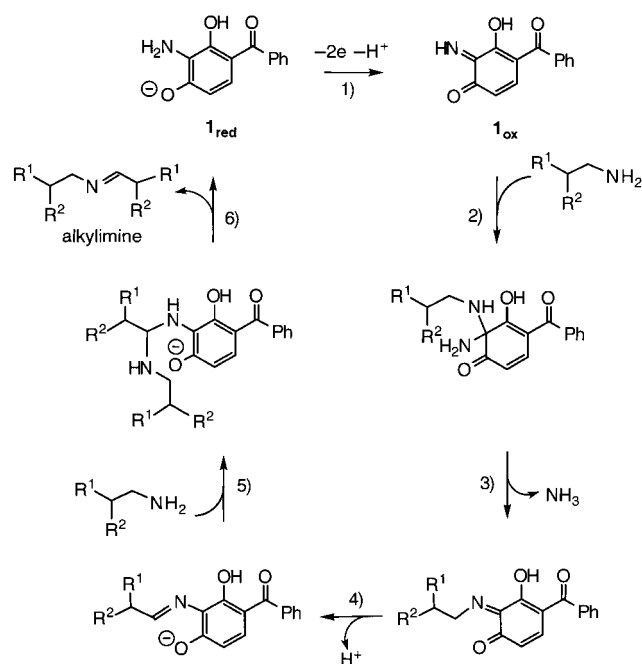
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Regiospecific Inverse-Electron-Demand Diels–Alder Reaction of Simultaneously Electrogenerated Diene and Dienophile: An Expeditious Route to Polyfunctionalized 1,4-Benzoxazine Derivatives

Martine Largeron,* Anne Neudorffer, Marc Vuilhorgne, Estelle Blattes, and Maurice-Bernard Fleury

Quinonoid systems are powerful intermediates for organic synthesis and constitute potential precursors to numerous naturally occurring substances.^[1] However, the synthesis of quinonoid entities, particularly *o*-quinones and *o*-azaquinones, which are usually unstable and very prone to polymerization, is not highly developed.^[2] The facile generation of *o*-quinone-type structures by the electrochemical oxidation of related *o*-quinols and their well-known ability to react with nucleophiles^[3] prompted us to investigate the reaction of highly reactive electrogenerated *o*-quinone species with amino alcohols, and we recently described the one-pot electrochemical synthesis of substituted 1,4-benzoxazine derivatives, a novel class of potent neuroprotective agents.^[4]

We also revealed a new mode of reactivity of these quinonoid systems,^[5] in which electrogenerated 3,4-azaquinone **1_{ox}** (Scheme 1) acts as an efficient catalyst for the



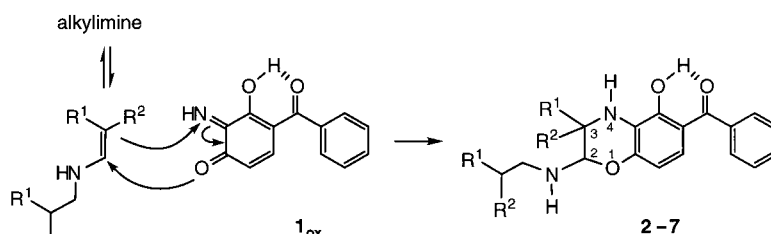
Scheme 1. Mechanism of catalytic oxidation of primary aliphatic amines mediated by electrogenerated model quinonoid cofactor **1_{ox}**.

[*] Dr. M. Largeron, Dr. A. Neudorffer, Dr. M. Vuilhorgne,^[†] E. Blattes, Prof. M.-B. Fleury
Laboratoire de Chimie Analytique et Electrochimie
UMR 8638 CNRS - Université René Descartes
Faculté des Sciences Pharmaceutiques et Biologiques
4, Avenue de l'Observatoire, 75270 Paris Cedex 06 (France)
Fax: (+33)01-43-29-05-92
E-mail: largeron@pharmacie.univ-paris5.fr

[†] Aventis Pharma, Centre de Recherche de Vitry-Alfortville
13, quai Jules Guesde, 94403 Vitry-sur-Seine (France)

autorecycling oxidation of benzylamine, in a way reminiscent of that reported for amine oxidoreductase model cofactors; the reaction efficiency reached 64 turnovers. Through electrochemical investigations, we established that the deamination mechanism of benzylamine by our model cofactor **1_{ox}** was related to the transamination reaction of pyridoxal phosphate with amino acids. The catalytic cycle produced the reduced catalyst **1_{red}** and *N*-benzylidenebenzylamine as the product of benzylamine oxidation (Scheme 1). The potent reactivity of **1_{ox}** was extended further to unactivated primary aliphatic amines. In several cases (e.g. isopentylamine), the reaction efficiency reached 50 turnovers. Such a reactivity has not yet been reported with other existing amine oxidoreductase model cofactors under similar conditions.^[6] In contrast, in the case of isobutylamine, the reaction efficiency did not exceed 8 turnovers, which agrees with an untimely deterioration of the catalyst **1_{ox}**. Herein, we demonstrate that *o*-azaquinone **1_{ox}** is a willing partner in inverse-electron-demand Diels–Alder reactions with simultaneously electrogenerated putative enamines (Scheme 2). To the best of our knowledge, this reaction is the first example of an intermolecular Diels–Alder reaction^[7] of electron-rich dienophiles with an *o*-quinone imine, though similar reactions with *o*-quinone monoimides^[8] and *o*-quinone monooximes^[9] are known. This unexpected reaction, in which the diene and the dienophile are simultaneously electrogenerated, provides an expeditious route to new polyfunctionalized 1,4-benzoxazine derivatives.

3,4-Iminoquinone **1_{ox}** was electrogenerated from 3,4-aminophenol **1_{red}**, by using anodic-controlled potential electrolysis, at a mercury electrode, in methanol that contained excess primary aliphatic amine $\text{NH}_2\text{CH}_2\text{CHR}^1\text{R}^2$. At the potential at which the 3,4-aminophenol **1_{red}** could be oxidized to the iminoquinone form **1_{ox}** (see Experimental Section), the anodic current remained unchanged for some time, which is consistent with steady-state catalytic behavior. This indicated that our catalyst **1_{ox}** was able to oxidize unactivated primary aliphatic amines to the corresponding alkylimines, according to the transamination mechanism shown in Scheme 1.^[5] However, the catalytic process ceased after 6 to 8 turnovers. Close inspection of the exhaustively oxidized solution revealed that electrogenerated 3,4-iminoquinone **1_{ox}** was trapped with the tautomeric enamine form of the alkylimine extruded during the catalytic process (Scheme 1, step 6), to give the substituted 1,4-benzoxazine derivatives in good to high yields (52–77%). Table 1 shows some examples of the molecular diversity that is accessible through this reaction, which is an inverse-electron-demand controlled Diels–Alder reaction between the LUMO of the *o*-azaquinone heterodiene and the HOMO of the enamine. This uncatalyzed cycloaddition reaction occurs at room temperature, within 8 h, with complete regioselectivity. The more electron-rich carbon atom of the enamine dienophile adds to the nitrogen atom of the heterodiene system **1_{ox}** (Scheme 2, Table 1). Accordingly, alkylamines with a pronounced electron-rich character led to the formation of the expected cycloadduct in high yields (Table 1, entries 1–4), whereas enamines that bear



Scheme 2. Diels–Alder reaction of enamine dienophiles with *o*-azaquinone diene **1_{ox}**, electrogenerated simultaneously, to give polyfunctionalized 1,4-benzoxazine derivatives.

Table 1. Inverse-electron-demand Diels–Alder reactions of simultaneously electrogenerated diene and enamine dienophile.

Entry	Enamine	Product	Yield [%]
1			71
2			70 ^[a]
3			77
4			70
5			55
6			52 ^[a]

[a] Obtained as a mixture of two unassigned diastereoisomers (ca. 1:1 ratio).

phenyl substituents resulted in somewhat lower yields (Table 1, entries 5 and 6).

No subsequent elimination of the alkylamino chain was observed, in contrast to what has been previously reported for similar cycloadditions of enamines with heterodienes.^[10] This feature is of synthetic interest since the methodology we describe herein represents the first synthesis of 1,4-benzoxazine derivatives that bear alkylamino substituents on the oxazine ring.

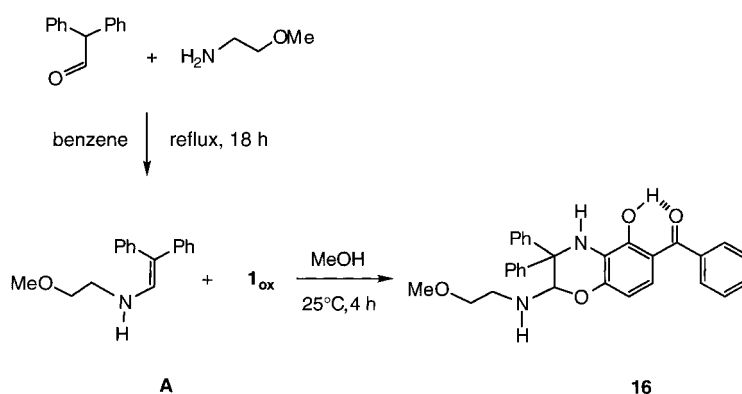
In a second series of experiments aimed at increasing the molecular diversity, we attempted to generate enamines in

which the substituents on the amino group were different from those linked to the double bond. For this purpose, the amine $R^1R^2CHCH_2NH_2$ was catalytically oxidized by *o*-azaquinone **1_{ox}** in the presence of another primary aliphatic amine R^3NH_2 . Table 2 gives some examples of 1,4-benzoxazine derivatives produced in this way. The choice of amines proved to be important for the outcome of the reaction, which is affected by steric and electronic effects exerted by the substituents R^1 , R^2 , and R^3 . In particular, the most nucleophilic amine was oxidized, except when prevented by steric hindrance (Scheme 1, step 2). In all cases, both reacting amines were used in equimolar quantities and no efforts were made to optimize the yield. Further investigations would be necessary to establish the optimal reaction conditions.

Table 2. Catalytic oxidation of amine $R^1R^2CHCH_2NH_2$ by *o*-quinone imine **1_{ox}** in the presence of a second amine R^3NH_2 .

Entry	Enamine	Product	Yield [%]
1			70 ^[a]
2			50
3			68 ^[b]
4			33
5			60
6			41
7			66 ^[a,b]
8			62 ^[b]

[a] Obtained as a mixture of two unassigned diastereoisomers (ca. 1:1 ratio).
 [b] Beside benzoxazines **10**, **14**, and **15**, benzoxazines **2**, **3**, and **4** were isolated as minor products, in yields of 5, 10, and 20 %, respectively.



Scheme 3. Cycloaddition of enamine **A** and the electrogenerated *o*-azaquinone diene **1_{ox}**, prepared separately.

Finally, the reaction of a separately prepared enamine with the electrogenerated *o*-azaquinone diene **1_{ox}** was demonstrated in a control experiment. For this purpose, 2,2-diphenylacetaldehyde and 2-methoxyethylamine were condensed to produce enamine **A** (Scheme 3). This was reactive enough to combine with the fairly labile electrogenerated azaquinone **1_{ox}** before its oligomerization, thus allowing the isolation of the 1,4-benzoxazine derivative **16** in 51 % yield (see Experimental Section). Interestingly, this methodology that uses a separately prepared enamine should expand the scope of the reaction as it would no longer be limited to the enamine part that originates from the more nucleophilic amine (Table 2).

In summary, we have demonstrated that putative enamines^[11] and unstable *o*-azaquinone **1_{ox}**, which are simultaneously accessible by an electrochemical process, cyclize at room temperature with complete regioselectivity in the absence of catalyst, to afford new polyfunctionalized 1,4-benzoxazine derivatives in a one-pot synthesis. As a result of their structural similarity with 1,4-benzoxazines reported earlier,^[4] these compounds could be considered as target structures for the design of novel neuroprotective agents.

Experimental Section

General procedure: Controlled-potential electrolysis was carried out in a cylindrical, three-electrode, divided cell (9 cm diameter) by using an electronic potentiostat. In the main compartment, a mercury pool electrode (60 cm² area) served as the anode (working electrode). Alternatively, a platinum grid (6 cm diameter) could be used as the anode, except with phenyl substituted aliphatic amines, due to a platinum electrode fouling problem. A platinum sheet was placed in the concentric cathodic compartment (counter electrode), which was separated from the main compartment with a glass frit. The reference electrode was an aqueous saturated calomel electrode (SCE), which was isolated from the bulk solution in a glass tube with a fine-porosity frit. The electrolyte solution (0.02 mol L⁻¹ tetraethylammonium perchlorate (TEAP) in methanol) was poured into the anodic and the cathodic compartments, as well as into the glass tube that contained the SCE electrode. 3,4-Aminophenol **1_{red}** (0.5 mmol) and excess primary aliphatic amine $R^1R^2CHCH_2NH_2$ (10 mmol), or a mixture of amine $R^1R^2CHCH_2NH_2$ (5 mmol) and amine R^3NH_2 (5 mmol), were added to the solution in the main compartment (250 mL), and the resulting solution was then oxidized under nitrogen, at room temperature, at +50 mV vs SCE (initial current 50 mA), that is, at a potential following the anodic peak observed in cyclic voltammetry, characteristic of the two-electron oxidation of **1_{red}** to **1_{ox}**. After exhaustive electrolysis (8–10 h, 12 to 16 Faraday mol⁻¹), that is, when a negligible value of the current was recorded (1 mA), the solution was neutralized with dry ice and the solvent

was removed under reduced pressure. The brown oil residue was then poured into diethyl ether (20 mL). Insoluble TEAP was filtered off and the filtrate was evaporated under reduced pressure, at 30 °C. Flash chromatography of the residue on silica gel afforded the expected 1,4-benzoxazine derivative.

16: A mixture of 2,2-diphenylacetaldehyde, 2-methoxyethylamine (slight excess), and toluene-*p*-sulfonic acid (catalytic amount) was heated at reflux in benzene for 18 h. The water was removed initially by means of a Dean–Stark separator, and then by using a molecular sieve. The solvent was removed under reduced pressure and the residue distilled. The freshly distilled enamine **A** (2.5 mmol) was dissolved in methanol (250 mL) that contained TEAP as the supporting electrolyte (5 mmol). 3,4-Aminophenol **1_{red}** (0.5 mmol) was then added to the resulting solution, along with 2-methoxyethylamine (0.5 mmol). The addition of the latter was necessary to produce the monoanionic species of **1_{red}**, which is the sole form that can be oxidized to *o*-azaquinone **1_{ox}**.^[5] The resulting solution was then oxidized, under nitrogen, at room temperature, at a mercury pool whose potential was fixed at +50 mV vs. SCE. After exhaustive electrolysis (4 h, 2.1 Faraday mol⁻¹), the solution was treated as above (general procedure) to give the 1,4-benzoxazine derivative **16** in 51 % yield.

2: M.p. 133 °C; ¹H NMR (300 MHz, CDCl₃): δ = 0.85 (d, *J* = 6 Hz, 3 H), 0.90 (d, *J* = 6 Hz, 3 H), 1.25 (s, 3 H), 1.30 (s, 3 H), 1.70 (m, *J* = 6 Hz, 1 H), 1.90 (s, 1 H), 2.50 (m, 1 H), 2.80 (m, 1 H), 4.00 (s, 1 H), 4.65 (s, 1 H), 6.40 (d, *J* = 9 Hz, 1 H), 7.00 (d, *J* = 9 Hz, 1 H), 7.50 (m, 3 H), 7.65 (m, 2 H), 12.8 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃): δ = 20.3, 24.5, 26.3, 28.8, 50.2, 53.0, 92.9, 108.5, 112.6, 120.9, 124.0, 128.0, 128.8, 131.2, 138.4, 146.9, 152.0, 198.5; UV/Vis (methanol): λ_{max} (ε) = 258 (21 850), 320 (17 150); MS-DCI: *m/z*: 355 [MH⁺].

10: M.p. 110 °C; ¹H NMR (300 MHz, CDCl₃): δ = 1.25 (s, 3 H), 1.30 (s, 3 H), 2.10 (s, 1 H), 2.90 (dd, *J* = 6 Hz and *J* = 13 Hz, 1 H), 3.10 (dd, *J* = 6 Hz and *J* = 13 Hz, 1 H), 3.35 (s, 6 H), 4.00 (s, 1 H), 4.45 (t, *J* = 6 Hz, 1 H), 4.70 (s, 1 H), 6.40 (d, *J* = 9 Hz, 1 H), 7.00 (d, *J* = 9 Hz, 1 H), 7.50 (m, 3 H), 7.65 (m, 2 H), 12.70 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃): δ = 24.5, 26.3, 47.1, 50.2, 53.4, 54.1, 92.5, 104.2, 108.5, 112.8, 121.0, 123.9, 128.1, 128.9, 131.2, 138.5, 147.1, 152.1, 201.0; UV/Vis (methanol): λ_{max} (ε) = 258 (21 670), 319 (17 050); MS-DCI: *m/z*: 387 [MH⁺].

16: M.p. 190 °C; ¹H NMR (300 MHz, CDCl₃): δ = 2.50 (s, 1 H), 3.00 (m, 1 H), 3.10 (m, 1 H), 3.20 (s, 3 H), 3.35 (t, *J* = 6 Hz, 2 H), 5.20 (s, 1 H), 5.80 (s, 1 H), 6.35 (d, *J* = 9 Hz, 1 H), 6.95 (d, *J* = 9 Hz, 1 H), 7.20 to 7.55 (m, 13 H), 7.65 (m, 2 H), 12.90 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃): δ = 45.0, 58.6, 62.4, 72.6, 89.7, 108.8, 112.8, 120.8, 124.6, 126.6, 126.9, 127.0, 128.1, 128.2, 128.4, 128.9, 131.3, 143.0, 144.3, 147.2, 152.3, 200.6; UV/Vis (methanol): λ_{max} (ε) = 258 (21 950), 319 (17 200); MS-DCI *m/z*: 481 [MH⁺].

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Voltage-Driven Changes in Molecular Dipoles Yield Negative Differential Resistance at Room Temperature**

Yoram Selzer,* Adi Salomon, Jamal Ghabboun, and David Cahen*

The effect of negative differential resistance (NDR), discovered by Esaki^[1] in Ge *p*–*n* diodes, forms the basis for a variety of high-speed semiconductor devices.^[2] As future generations of electronics may rely on molecules as part of intelligent and/or nanoscopic devices,^[3] much attention is given to the idea of molecular NDR. Experimentally only a few NDR devices utilizing molecules as the active component, have been reported.^[4–10] Except for one,^[10] all were effective only at low temperature (*T* < 78 K) and under high-vacuum conditions. Herein we report molecule-controlled, room-temperature NDR in a metal/molecular layer/semiconductor diode in ambient atmosphere.

The diodes use a series of relatively simple molecules of the type depicted in Figure 1. Hg was used as the metal and *p*-Si as the semiconductor because:

- 1) Disulfide molecules are electrochemically active once adsorbed on Hg.^[11]

[*] Dr. Y. Selzer, Prof. D. Cahen, A. Salomon, J. Ghabboun
Department of Materials & Interfaces
Weizmann Institute of Science
Rehovot 76100 (Israel)
Fax: (+972) 8-934-4139
E-mail: yus1@email.psu.edu, david.cahen@weizmann.ac.il

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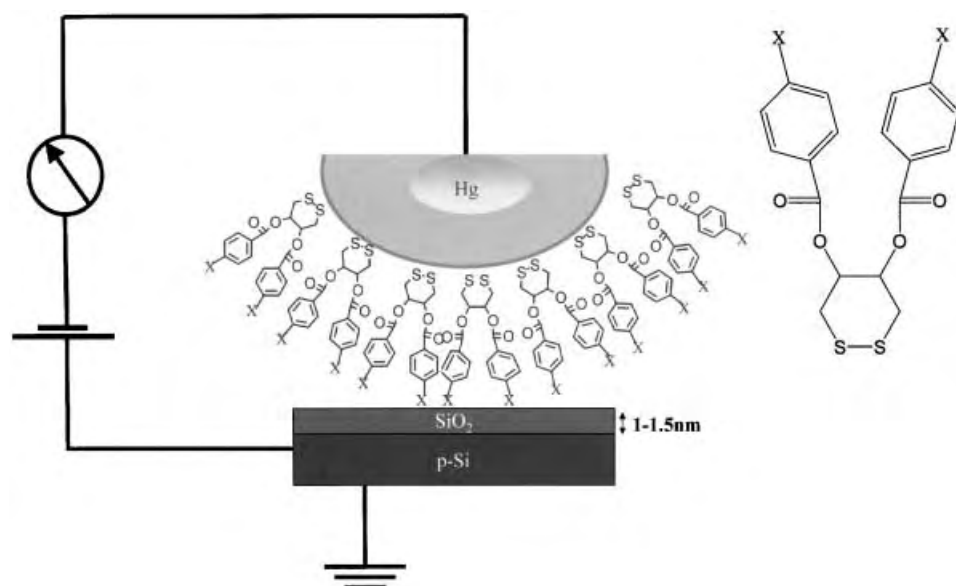


Figure 1. A schematic picture of the junction, and the dipolar molecules used. X = CF₃, CN, H, OMe.

- 2) Hg can be applied simply as a top contact to relatively large molecular junctions.^[12–15]
- 3) Hg is known not to react with Si and SiO_x surfaces.^[16]
- 4) Hg makes a blocking contact with p-Si.

Junctions were assembled using clean-room facilities and modifying various stages from previously reported procedures.^[12–15] Characterization of the molecular monolayers used here, which included ellipsometry on Au, were reported by us earlier.^[17] A typical set of experimental current–voltage (*I*–*V*) curves is shown in Figure 2. The largest NDR was measured for molecules with a CF₃ end group. Such devices had a peak current density > 2 A cm^{–2}, NDR < –490 μΩ m², and a peak to valley ratio of 25:1, the best room-temperature NDR characteristics reported for a molecule-based device.

The effect of the other dipoles on *I*–*V* curves is less pronounced, with NDR decreasing as the substituents on the molecules change from CF₃ to CN to H to CH₃O. We postulate that the observed trend is a result of two contributions, namely, different Schottky barrier heights and voltage driven change in charge transmission.

Different Schottky barrier heights: Similar to what we have reported on earlier,^[18–20] the potential across Schottky junctions can be tuned by assembling monolayers made up of molecules with different dipole moments at the interface. The change in potential is manifested as a change in the barrier height inside the semiconductor, Φ_b . This dipole effect is demonstrated here for the first time on a p-type semiconductor. To a first approximation, the barrier height of a

p-type semiconductor is given by [Eq. (1)],^[21] where E_g is the band gap of the semiconductor, χ_{sc} is its electron affinity, Φ_m is the work function of the metal (prior to modification) and Φ_{dipole} is the electrostatic potential step associated with the film of molecular dipoles.

$$\Phi_b = E_g + \chi_{sc} - (\Phi_m + \Phi_{dipole}) \quad (1)$$

A dipole layer that effectively increases the metal's work function should decrease the barrier height, after contact is made with a semiconductor. The opposite effect is expected if the dipole layer decreases the metal's work function. The experimental results (see insert of Figure 2, and Table 1) support this: junctions

containing molecules with dipoles for which $\Phi_{dipole} > 0$, that is, with CF₃ or CN substituents, have a lower effective barrier height than those with molecules, containing –H or –CH₃O substituents, for which $\Phi_{dipole} < 0$. Samples without molecules

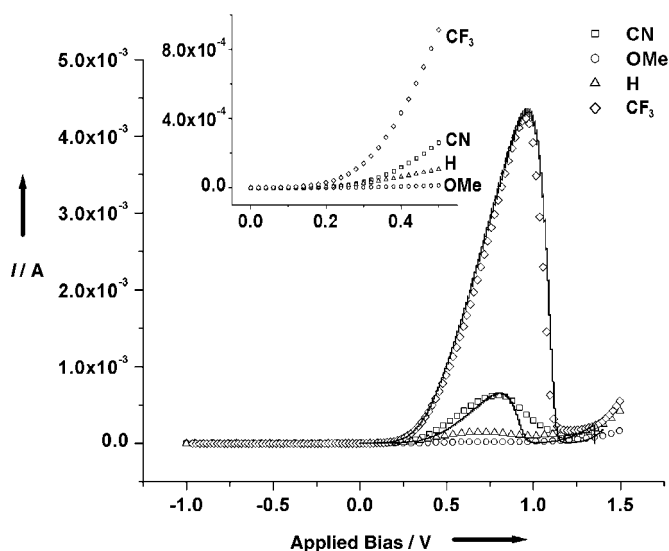


Figure 2. Experimental *I*–*V* curves for junctions of Figure 1, with the different dipolar molecules. For the sake of clarity simulated results (continuous lines) are shown only for the junctions with CF₃- and CN-substituted molecules. Insert: The low voltage (pre-NDR) range, of the *I*–*V* curves, which shows the effect of the molecular dipole moments on the barrier height of junctions, as described in detail in refs. [18–20].

Table 1. Parameters extracted from *I*–*V* curves and related data. Dipole values were calculated by ab initio methods. Φ_b and V^{NDR} were extracted from the experimental curves. Δ and V^0 were the fitting parameters (see text).

End group	Dipole moment [D] ^[a]	Φ_b [V]	Δ [eV]	V^0 [V]	V^{NDR} [V]	Anion dipole moment [D] ^[a]
CF ₃	0.9	0.36	2.70	0.80	0.92	–1.1
CN	0.4	0.38	1.50	0.60	0.80	–13.4
H	–5.4	0.40	0.95	0.43	0.71	–15.9
CH ₃ O	–6.6	0.44	0.45	0.43	0.70	–16.6

[a] Negative dipole values are used to describe dipoles having their negative pole pointing to the metal surface.

do not show NDR and give $I-V$ curves with higher currents because of the lack of a molecular layer (cf. ref. [18]).

Voltage driven change in charge transmission: NDR behavior in our system depends critically on that, upon adsorption on Hg, the cyclic disulfide end of the molecules can undergo a redox reaction [Eq. (2)].^[11]



Several control experiments verified that indeed the disulfide bond is the electrochemically active part of the molecules:

- 1) Junctions made with simple thiols adsorbed on mercury did not show NDR behavior.
- 2) Cyclic disulfide molecules with long alkyl chains instead of benzene rings showed NDR behavior (see below); thus, the active part of the system is not one of the rings.
- 3) The same dipole molecules adsorbed on gold do not show NDR behavior,^[19] in agreement with literature data that suggest that disulfide bonds are broken upon their adsorption on gold.^[22]

The junctions that we deal with are between a metal and a p-type semiconductor which means that under forward bias conditions the Hg atoms are negative with respect to the Si ones. As the forward bias voltage is increased it reaches a value that is sufficiently negative (with respect to the Si) to drive the reduction in Equation (2). This reaction can occur at the interface as no other reagents are needed, there are no products to be removed, and because the necessary electrostatic screening, normally provided by solvent molecules or counterions, is supplied by image charges on the metal.

The two added electrons are mainly localized on the sulfur atoms.^[23] This localization results from:

- 1) The electronegativity of sulfur.
- 2) That the reduced disulfide bond is not conjugated to the rest of the molecule.
- 3) There is good screening of the disulfide bond by the metal (see above).

As one side of the interface is a semiconductor, extra charge at the interface will normally lead to realignment of the semiconductor energy-band positions, with respect to the metal Fermi level, to change the band bending and thus produce a new barrier height, Φ_b , inside the semiconductor. However, since in our case (see Table 1), the reduction in Equation (2) occurs at forward bias potentials that are higher than the barrier height, that is, with no depletion left in the semiconductor, it is likely that the observed NDR results from a change in tunneling probability, rather than from a change in Φ_b .

The localized charges reduce the charge transmission across the junction by creating a potential barrier at the ends of the molecules.^[24–27] Electrons essentially have to tunnel through this potential barrier that can be as high as a few eV. As more molecules are reduced, charge transmission becomes less efficient and the $I-V$ curve collapses to a curve with lower current characteristics, establishing the NDR effect.

We have semi-quantitatively simulated this process assuming that:

- 1) The governing mechanism of charge transfer in our devices is thermionic emission.^[2]

- 2) The reaction in Equation (2), the process by which the dipoles are changed, can be treated using Laviron's methodology for surface-bound electrochemical reactions.^[28]
- 3) Since the molecules are not conjugated, with a free-molecule HOMO–LUMO gap in the order of 7 eV,^[23, 29] tunneling is assumed to be nonresonant with, as a first approximation, the tunneling probability defined for a rectangular potential barrier.^[2] The width of the barrier was taken as 2.5 nm, based on ellipsometry measurements of the SiO₂ (1.5 nm) and of the molecular monolayers (1 nm, see reference [17]).

Fitting of simulations could be carried out by varying only two parameters, the maximal change in tunneling barrier, Δ , and V^0 the “standard reduction potential” of the disulfides. The barrier height, Φ_b , and V^{NDR} , the onset potential of NDR were extracted from the experimental curves.^[30]

The different parameters are summarized in Table 1. From this we see that:

- 1) There is excellent qualitative agreement between the trend seen in the onset potentials of NDR (calculated by differentiating the $I-V$ curves) and the standard redox potentials, V^0 , of Equation (2) that were used as fitting parameters. The onset potentials are shifted relative to the V^0 values, because of the irreversibility of the reduction process.^[28]
- 2) The added barrier for tunneling correlates well with the calculated dipoles for the anions that are produced by reduction in Equation (2). Internal electrostatic fields are known to affect the rates of charge transfer.^[31, 32] In general, electron transfer in the direction of a permanent dipole ($\delta^+ \rightarrow \delta^-$) is slower than the rate of electron transfer in a direction that opposes the dipole. In our case, the molecules with the electron withdrawing groups, that is, CF₃ and CN, have the highest opposing field to electron transfer from the Hg to the p-Si. The dipole with the CF₃ substituent produces the strongest NDR because this dipole produces the biggest change in junction properties, that is, from initial smallest Schottky barrier to final lowest tunneling probability (see Table 1).

The devices age as a consequence of repeated cycling and the NDR effect usually disappears after 3–4 cycles.^[33] This effect is probably because of complete random disorientation of the molecules after detachment from the mercury following reduction [Eq. (2)]. Structural rearrangements at interfaces have been shown to exist even in highly ordered monolayers.^[34] Rearrangements at our interfaces are probable because the molecules used are too short to allow their assembly into highly ordered monolayers. Indeed, we know from previous studies that layers of this type of disulfide molecules are not highly ordered.^[17] To test this, we made a device based on a similar molecule with long alkyl chains instead of the benzene rings. This molecule, monolayers of which on Au were found to be twice as thick (2 nm) as those of the molecules shown in Figure 1 (1 nm^[17]) gives a more ordered monolayer than the other cyclic disulfide species used here.^[17] The resulting $I-V$ curves in Figure 3 show that after several cycles the junction becomes stable without any further degradation. Initial aging probably results from some structural rearrangements in the vicinity of defects in the monolayer.

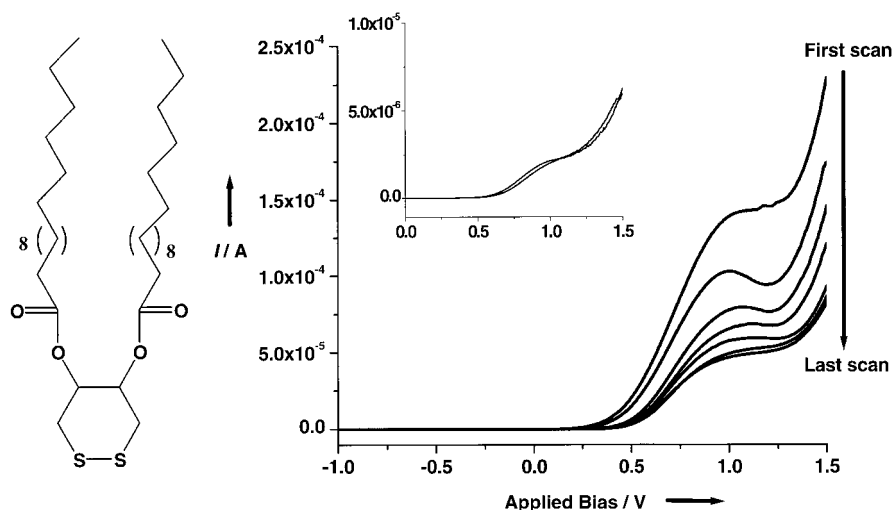


Figure 3. I – V curves of a device, made with molecules similar to those used for Figure 1, but with long aliphatic chains (left). These molecules pack in a relatively ordered monolayer. After some initial degradation in their I – V curves, such devices show stable “NDR-like” characteristics as can be seen in the insert, which shows the I – V curves of a device under continuous cycling.

The above results suggest a new mechanism for controllable NDR in molecule-controlled devices. The diversity of electro-switchable dipole molecules that can be prepared makes this new approach a promising tool for tailor-made NDR devices.

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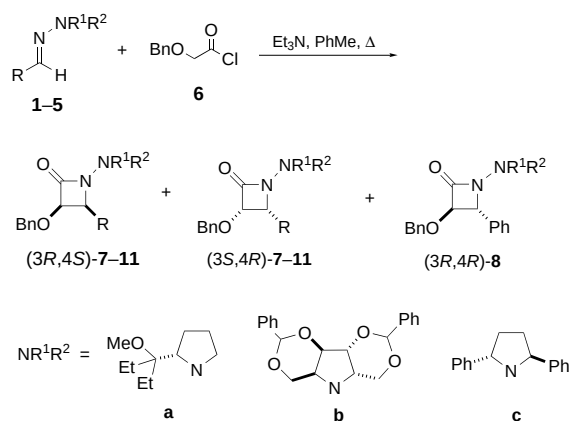
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N,N-Dialkylhydrazones as the Imine Component in the Staudinger-Like [2+2] Cycloaddition to Benzyloxyketene**

Rosario Fernández, Ana Ferrete, José M. Lassaletta,*
José M. Llera,* and Eloísa Martín-Zamora

The presence of a β -lactam ring as a key substructure of the most widely used family of antibiotics has stimulated considerable activity focused on the development of stereoselective routes for its synthesis.^[1] One of the most popular methods involves the [2+2] cycloaddition of ketenes and imines (the Staudinger reaction),^[2] but this straightforward method suffers limitations imposed by the poor stability of some imines, such as methanimines (unstable against polymerization) and those derived from aliphatic aldehydes (easily enolizable and thermally unstable). Previously, we reported the use of formaldehyde *N,N*-dialkylhydrazones as a stable class of monomeric methanimines in the asymmetric Staudinger [2+2] cycloaddition to α -alkoxy- and α -amino ketenes.^[3] Stimulated by the promising results obtained in this particular case, we decided to investigate also the behavior of higher aldehyde *N,N*-dialkylhydrazones as a stable class of enolizable imines in the same context.

Considering the lack of general approaches for the enantioselective synthesis of 4-alkyl(aryl)-3-hydroxy- β -lactams and their potential as precursors of bioactive β -amino- α -hydroxy acids,^[4] we focused on the [2+2] cycloaddition of chiral aldehyde hydrazones to α -benzyloxyketene (Scheme 1). Studies started with the reaction of proline-derived hydrazones **1a–5a** with benzyloxyacetylchloride **6** which leads to the desired cycloadducts **7a–11a**, respectively, in excellent yields (84–98%), even for compounds derived from easily enolizable substrates (Table 1, entries 1–4). Under optimized conditions (toluene, Et₃N, 80 °C for primary substrates, 100 °C for secondary or aromatic substrates), moderate to good 3*R*,4*S*/3*S*,4*R* selectivities were found, and only traces of *trans* isomers were detected in some cases. Nevertheless, the collected results were satisfactorily evaluated because the diastereomers could be separated easily in all cases, thus allowing the isolation of the optically pure major *cis* isomers (3*R*,4*S*)-**7a**–(3*R*,4*S*)-**11a** in yields of 70–82%.



Scheme 1. [2+2] Cycloadditions of *N,N*-dialkylhydrazones to benzyloxyketene. **1**: R = *n*-pentyl, **2**: R = *i*Bu, **3**: R = PhCH₂CH₂, **4**: R = *i*Pr, **5**: R = Ph. Bn = benzyl.

Table 1. Synthesis of 1-*N,N*-dialkylamino-3-benzyloxyazetidin-2-ones **7a–11a**, **11b**, and **8c**.

Entry	Hydrazones	<i>T</i> [°C]	Product	Yield [%] ^[a]	3 <i>R</i> ,4 <i>S</i> : 3 <i>S</i> ,4 <i>R</i> ^[b]	<i>cis</i> : <i>trans</i> ^[b]
1	1a	80		85 (70)	82:18	98:2
2	2a	80		84 (73)	87:13	98:2
3	3a	80		97 (78)	80:20	> 99:1
4	4a	100		90 (82)	91:9	> 99:1
5	5a	100		98 (75)	76:24	> 99:1
6	5b	100		66	< 1:99	> 99:1
7	2c	80		53	> 99:1	90:10

[a] Yield of isolated product. Values in parentheses correspond to the pure (98% *de*) major isomer. [b] Determined by means of ¹³C and ¹H NMR spectroscopy.

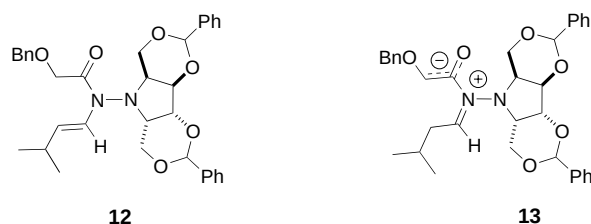
[*] Dr. J. M. Lassaletta
Instituto de Investigaciones Químicas (CSIC-USé)
Americo Vespuccio s/n
Isla de la Cartuja, 41092 Seville (Spain)
Fax: (+34)95-446-0565
E-mail: jmlassa@cica.es

Dr. E. Martín-Zamora, Dr. R. Fernández, A. Ferrete
Dpto. de Química Orgánica
Universidad de Sevilla (Spain)

Dr. J. M. Llera
Dpto. de Química Orgánica y Farmacéutica
Universidad de Sevilla (Spain)
Fax: (+34)95-423-3765
E-mail: llera@fajar.us.es

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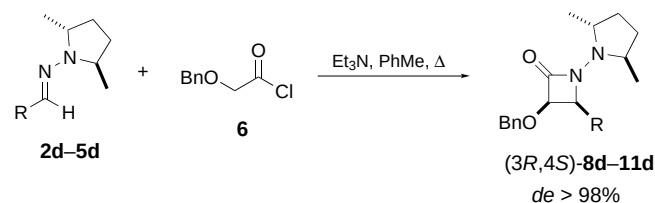
The behavior of D-mannitol-derived hydrazones^[3] was studied next. However, the reaction of isobutyraldehyde hydrazone **2b** with **6** afforded only compound **12** under a



variety of reaction conditions, thus suggesting that an intramolecular H transfer in the zwitterionic intermediate^[5] **13** takes place faster than the ring closure to the β -lactam. On the other hand, the non-enolizable hydrazone **5b** reacted with **6** under forcing conditions, to give the desired β -lactam **11b** in a moderate yield (66%), but with excellent stereoselectivity (Table 1, entry 6). From these results, it appears that the mannitol-derived C_2 -symmetric auxiliary offers better induction in the cycloaddition process than the proline-derived auxiliary (Table 1, entries 5 and 6), but the lower reactivity of the former prevents a better result. Considering that steric factors would hardly explain the observed differences in behavior, the lack of conformational flexibility in **5b**, associated with the condensed dioxane rings, was seen as a possible reason.

Therefore, a more flexible C_2 -symmetric hydrazone such as **2c**, which has (2*S*,5*S*)-diphenylpyrrolidine as the auxiliary, was synthesized^[6] and treated with **6**. The desired cycloadduct **8c** was obtained with an excellent (3*R*,4*S*/3*S*,4*R*) selectivity (Table 1, entry 7), thus supporting the validity of the hypothesis mentioned above, but the yield (53%) was disappointing, and the product was contaminated with approximately 10% of the undesired *trans*-3*R*,4*R* diastereomer. The moderate reactivity of this system was attributed to a higher steric hindrance around the C=N bond, but the suitability of C_2 -symmetric auxiliaries in this context was confirmed again in view of the exhibited selectivity.

An ultimate attempt to improve the results obtained with hydrazones **1a–5a** was therefore based on the strategy outlined above, but with substrates that contain the sterically less demanding (2*R*,5*R*)-dimethylpyrrolidine as the auxiliary. As expected, a higher reactivity was observed in the reactions of **2d–5d**^[7] with **6**, which proceeded smoothly to give the corresponding cycloadducts **8d–11d** in high yields and with excellent 3*R*,4*S*/3*S*,4*R* selectivities (Scheme 2, Table 2). In this



Scheme 2. [2+2] Cycloadditions using (2*R*,5*R*)-dimethylpyrrolidine as the auxiliary.

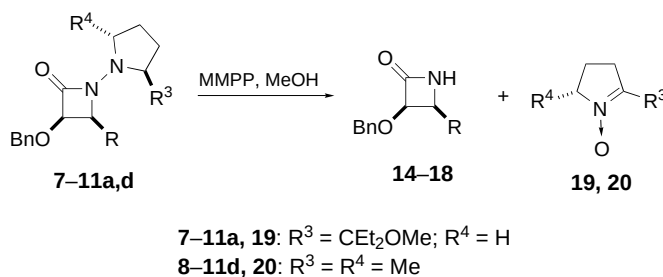
Table 2. Synthesis of 1-*N,N*-dialkylamino-3-benzyloxyazetidin-2-ones **8d–11d**.

Entry	Hydrazone	T [°C]	Product	Yield ^[a] [%]	3 <i>R</i> ,4 <i>S</i> : 3 <i>S</i> ,4 <i>R</i> ^[b]	<i>cis</i> : <i>trans</i> ^[b]
1	2d	60		70	> 99:1	95:5 ^[c]
2	2d	80		91	> 99:1	85:15
3	3d	rt		67	> 99:1	> 99:1
4	3d	60		83	> 99:1	> 99:1
5	3d	80		91	> 99:1	91:9
6	4d	80		80	> 99:1	> 99:1
7	5d	100		96	> 99:1	> 99:1

[a] Yield of isolated product. [b] Determined by means of ¹³C and ¹H NMR spectroscopy. [c] Inseparable mixture. The pure *cis* isomer was obtained after release of the auxiliary (see Table 3).

case, an optimum reaction temperature of 60 °C was applied to the reaction of **6** with aliphatic primary hydrazones **2d** and **3d** (Table 2, entries 1 and 4), since significant amounts of *trans* isomers appeared at 80 °C (Table 2, entries 2 and 5). The high reactivity of **2d–5d** allows cycloadditions even at room temperature (Table 2, entry 3), in contrast to all other hydrazones tested. Secondary (**4d**) and aromatic (**5d**) hydrazones reacted smoothly with **6** at optimized temperatures of 80 and 100 °C,^[8] to give the corresponding adducts **10d** and **11d** in 80 and 96% yield, respectively (Table 2, entries 6 and 7).

The key N–N bond cleavage, which is required to remove the auxiliaries, failed under standard reductive conditions. Fortunately, the oxidative method previously developed by our group^[3] was successfully applied to compounds **7a–11a** and **8d–11d**, which reacted with magnesium monoperoxyphthalate (MMPP) to afford the deaminated lactams (3*R*,4*S*)-**14–(3*R*,4*S*)-18** in high yields (Scheme 3, Table 3). Nitrones **19** and **20** were isolated as by-products from **7a–11a** and **8d–11d** in moderate (ca. 50%) and good (75–80%) yields,^[9] respectively.



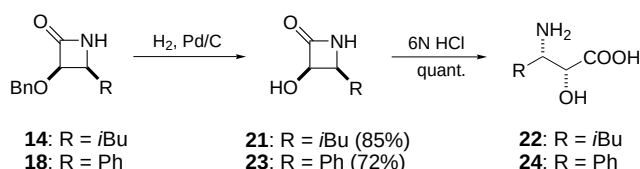
Scheme 3. Oxidative N–N bond cleavage. Release of the auxiliary.

Table 3. Synthesis of 4-alkyl(aryl)-3-benzyloxyazetidin-2-ones **14**–**18**.

Starting Material	<i>t</i> [h]	Product	Yield [%] ^[a]	$[\alpha]_D^{25}$ ^[b]
(3 <i>R</i> ,4 <i>S</i>)- 7a	3	(3 <i>R</i> ,4 <i>S</i>)- 14	78	+28.9
(3 <i>R</i> ,4 <i>S</i>)- 8a	2.5	(3 <i>R</i> ,4 <i>S</i>)- 15	91	+33.4
(3 <i>R</i> ,4 <i>S</i>)- 9a	2	(3 <i>R</i> ,4 <i>S</i>)- 16	87	+19.9
(3 <i>R</i> ,4 <i>S</i>)- 10a	4	(3 <i>R</i> ,4 <i>S</i>)- 17	88	+120.4
(3 <i>R</i> ,4 <i>S</i>)- 11a	2	(3 <i>R</i> ,4 <i>S</i>)- 18	96	+96.8
(3 <i>R</i> ,4 <i>S</i>)- 8d ^[c]	2	(3 <i>R</i> ,4 <i>S</i>)- 15	84 ^[d]	+33.5
(3 <i>R</i> ,4 <i>S</i>)- 9d	2	(3 <i>R</i> ,4 <i>S</i>)- 16	84	+20.9
(3 <i>R</i> ,4 <i>S</i>)- 10d	2	(3 <i>R</i> ,4 <i>S</i>)- 17	91	+120.6
(3 <i>R</i> ,4 <i>S</i>)- 11d	2	(3 <i>R</i> ,4 <i>S</i>)- 18	95	+97.3

[a] Yield of isolated product. [b] *c* = 1, Cl₂CH₂. [c] Starting material was a 9:1 mixture of *cis:trans* isomers. [d] Yield of pure *cis* product.

Finally, standard transformations of **18** and **14** afforded β -amino- α -hydroxy acids **24**, a side chain of taxol,^[10] and **22**, a component of the renin inhibitor KRI-1230^[11] and of the antitumor drug ABT-271,^[12] respectively (Scheme 4). These experiments served not only as illustrative examples of the synthetic utility of the method, but also confirmed the absolute configuration assigned to these compounds.^[13] The products with the opposite configuration could be also prepared by using the enantiomeric (2*S*,5*S*)-dimethylpyrrolidine^[14] as the auxiliary.



Scheme 4. Synthesis of β -amino- α -hydroxy acids.

In summary, the Staudinger cycloaddition of chiral *N,N*-dialkylhydrazones to benzyloxyketene appears to be a new general approach to the enantioselective synthesis of 4-substituted 3-alkoxyazetidin-2-ones. The (2*R*,5*R*)-dimethylpyrrolidine substituent is the key element in several aspects: 1) it confers the needed stability to the starting substrates, particularly in the aliphatic series; 2) it efficiently controls the stereochemical course of the reaction; and 3) it behaves as an efficient protecting group that can be removed easily from the β -lactam ring.

Experimental Section

7–11: Benzyloxyacetyl chloride (**6**, 4 mmol) in toluene (10 mL) was added stepwise (8 portions of 0.5 mmol over 3 h) to a solution of hydrazone **1–5** (1 mmol) and Et₃N (8 mmol) in dry toluene (5 mL). The mixture was stirred until completion and purified by chromatography.

14–18: MMPP·6H₂O (0.9 mmol) was added to a solution of **7–11** (0.3 mmol) in MeOH (0.75 mL), and the mixture was stirred at room temperature until completion.

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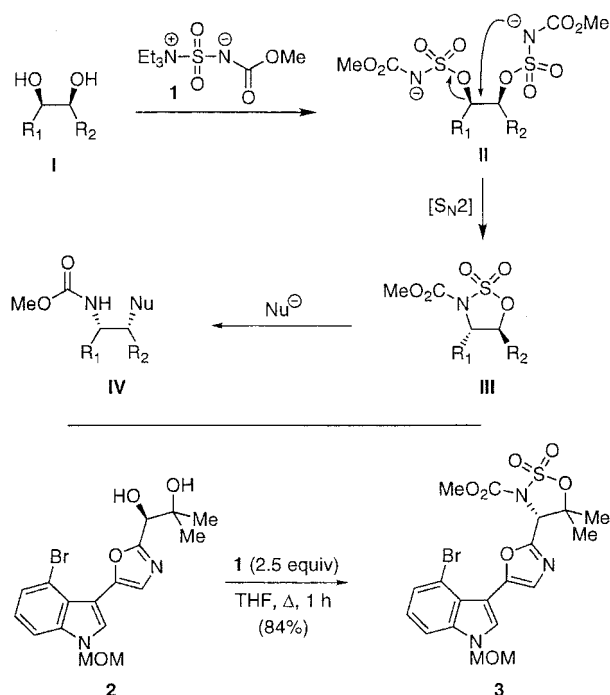
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A Novel Regio- and Stereoselective Synthesis of Sulfamides from 1,2-Diols Using Burgess and Related Reagents: A Facile Entry into β -Amino Alcohols**

K. C. Nicolaou,* Xianhai Huang, Scott A. Snyder, Paraselli Bheema Rao, Marco Bella, and Mali V. Reddy

Over the course of the past decade, chiral β -amino alcohols have become an increasingly targeted functional motif in organic synthesis owing to their ubiquity in biologically active compounds, as well as their value as ligands in asymmetric synthesis.^[1,2] Presently, several powerful methods exist to enantioselectively create such synthons, foremost of which is Sharpless' osmium-catalyzed asymmetric aminohydroxylation (AA).^[3] Although the utility of this reaction is unquestionable, variable regio- and enantioselectivity is still observed in certain structural types, despite significant optimization of reaction conditions.^[4,5] Herein we provide an alternative two-step approach for the regio- and stereoselective synthesis of a wide variety of 1,2-amino alcohols centered on initial construction of chiral sulfamides from enantiopure diols, orchestrated by Burgess reagent (**1**, Scheme 1), followed by mild treatment with aqueous acid. Furthermore, we disclose the development of several novel Burgess-type reagents which greatly extends the utility of this new protocol by enabling access to an orthogonal set of N-protected sulfamides.

Based on insight garnered during our program directed towards the total synthesis of the marine-derived natural product diazonamide A,^[6] we reasoned that it might be possible to generate a protected variant of a β -amino alcohol in the form of a cyclic sulfamidate (**III**) by exposing a diol (**I**) to excess Burgess reagent (**1**; Scheme 1).^[7] Although this chemical is typically employed as a powerful dehydrating reagent (for example, effecting the formation of olefins from alcohols),^[8] we envisioned that after the generation of an intermediate of type **II** from **I**, a unique and productive cyclization to sulfamidate **III** through the proposed S_N2



Scheme 1. Proposed conversion of diols **I** into cyclic sulfamidates **III** using Burgess reagent (**1**), and proof of principle (**2** → **3**). mom = methoxymethyl.

mechanism could potentially occur in preference to typical pathways that involve the loss of water. Assuming that this transformation proceeds with displacement of the more activated leaving group, then variation of the R¹ and R² substituents on enantiopure **I** would enable the stereo- and regioselective synthesis of diverse sulfamides.

Typically, sulfamides are prepared from chiral β -amino alcohol starting materials in several steps (based on the number of protecting-group manipulations required), and are then utilized to generate a diverse array of functionality based on the established ability of this synthon to undergo highly selective reactions with O-, S-, N-, C-, and F-based nucleophiles, to yield compounds of general structure **IV**.^[9] As such, the proposed synthesis of **III** would not only represent a more efficient approach than is currently available, since the nitrogen atom is concomitantly protected, but more significantly because the technology does not rely on the use of β -amino alcohol starting materials, it would provide a unique way to prepare this important functional motif stereoselectively from **III** simply by using water as a nucleophile. To test this hypothesis, we heated a THF solution of diol **2** (synthesized from the precursor olefin by dihydroxylation under standard conditions) and 2.5 equivalents of Burgess reagent (**1**)^[10] at reflux for 1 h and, most gratifyingly, observed the smooth formation of the desired sulfamidate **3** in 84% yield as a single regioisomer (>98:2) based on NMR spectroscopic analysis. Significantly, because attempted carbamate-based AA^[11] of **2** led to the desired product in modest yield with little control of regioselectivity, while the Ritter reaction under acidic conditions^[12] led solely to decomposition, the ease and selectivity of this particular Burgess-mediated transformation was suggestive of a potentially highly useful and applicable synthetic methodology.^[13]

[*] Prof. Dr. K. C. Nicolaou, Dr. X. Huang, S. A. Snyder, Dr. P. Bheema Rao, Dr. M. Bella, Dr. M. V. Reddy
Department of Chemistry and The Skaggs Institute
for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)

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We then sought to test the generality of this reaction process on a selection of styrene-derived diols that possessed a broad range of aromatic substitution patterns in an effort to explore the anticipated role of inductive effects on the regioselectivity of the S_N2 -based cyclization. We examined this particular class of compounds not only because it represents the best substrates for Sharpless asymmetric dihydroxylation (AD) in terms of both catalytic activity and enantioselectivity,^[14] but also because styrene-type olefins display good but variable yields and regioselectivity in carbamate-based AA.^[11] As shown in Table 1, Burgess-mediated sulfamidate synthesis followed the expected pattern for inductive influence in nucleophilic displacement at the benzylic position: electron-donating groups displayed excellent regioselectivity (Table 1, entries 1–4), whereas a lower selectivity was observed with electron-withdrawing substitu-

ents (Table 1, entries 6 and 7) relative to simple styrene (Table 1, entry 5). In all cases, the products were formed in high yield, and when two regioisomers were formed, the majority were separable by chromatography. Significantly, the poor regioselectivity observed in the conversion of **16** into **17** (Table 1, entry 7) was improved to 75:25 when the reaction was carried out at ambient temperature, albeit at the expense of yield (35 %).

To explore the role of steric encumbrance on the reaction process, and to test the applicability of the procedure for other structural classes, we explored several additional substrates (Table 2). As expected, increasing steric bulk at the terminal position of the styrene core with a single methyl group (Table 2, entries 1 and 2) dramatically increased the regioselectivity of cyclic sulfamidate formation (cf. Table 1). Surprisingly, substituents adjacent to the reactive benzylic center on the aromatic ring did not affect either yield or selectivity

Table 1. Regioselective synthesis of sulfamidates from diols by using Burgess reagent (**1**).

Entry	Starting material	Major product	Ratio of regioisomers ^[a]	Yield [%]
1			> 98:2	91
2			95:5	88
3			95:5	87
4			95:5	79
5			93:7	92
6			85:15	83
7			55:45	86

[a] Determined by means of ^1H NMR spectroscopic analysis of the crude reaction products.

Table 2. Further examples of the regioselective synthesis of sulfamidates from diols by using Burgess reagent (**1**).

Entry	Starting material	Major product	Ratio of regioisomers ^[a]	Yield [%]
1			> 98:2	72
2			95:5	87
3			> 98:2	92
4			> 98:2	94
5			85:15	82
6			> 98:2	81
7			71:29	41
8			> 98:2	76

[a] Determined by means of ^1H NMR spectroscopic analysis of the crude reaction products.

(Table 2, entries 3 and 4). Additionally, esters were well-tolerated in the reaction, with near complete regioselectivity observed for the formation of **29** from **28** (Table 2, entry 6), as a result of the mutually reinforcing effects of α -position deactivation by the ester moiety and the steric bulk imposed at that site by a methyl group. Competitive steric and electronic effects (Table 2, entry 7) led to retarded S_N2 displacement at the preferred terminal site, thereby reducing both regioselectivity and yield. Finally, reactions with simple aliphatic examples were highly regioselective, presumably because of the well-established preference for nucleophilic displacement of primary over secondary leaving groups. To verify the potential of this reaction for asymmetric synthesis, since all of the examples listed in Tables 1 and 2 were performed on racemic diol substrates, an X-ray crystal structure was obtained for sulfamidate **29** which confirmed that inversion of stereochemistry had occurred at the benzylic position relative to the racemic *cis*-diol starting material (Figure 1).^[15] Additionally, both racemic and enantiopure **26** were synthesized,^[16] and comparison of the chiral HPLC traces of the resultant products **27** indicated that preexisting stereochemical information was communicated in the reaction with complete fidelity.^[17]

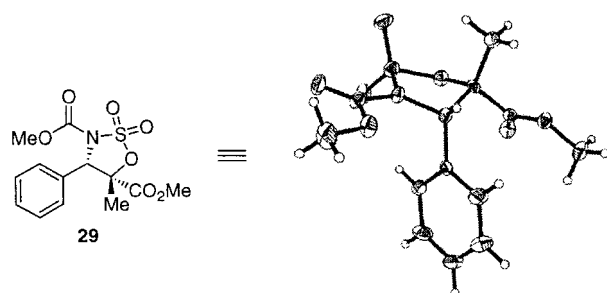
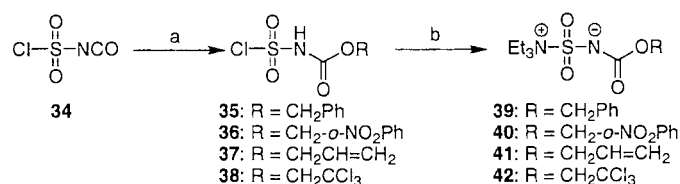


Figure 1. X-ray crystal structure of sulfamidate **29**.

To extend the overall utility of the present sulfamidate synthesis, we next sought to create compounds bearing N protection other than a methyl carbamate, a goal which could be achieved simply through modification of **1**. To our surprise, however, such reagents represented novel chemical entities, as an extensive search of the literature indicated that no efforts had been expended to create any Burgess-type salts other than those originally described almost thirty years ago. This result was unexpected, as **1** is known to pass both thermal and moisture sensitivity,^[8a] features which might be modulated by differentiation of the carbamate portion. We readily prepared four different Burgess-type reagents (**39–42**), representing an orthogonal set of amine protecting groups (based on deprotection by hydrogenation, photolysis, exposure to palladium-based catalysts, or treatment with Zn, respectively) simply by treating chlorosulfonylisocyanate (**34**) with the alcohol of interest, followed by subsequent exposure to Et₃N (Scheme 2). The relative ease of these preparations implies that virtually any carbamate-based Burgess-type salt can be accessed by this approach.^[18] Exposure of several diol substrates to **39–42** resulted in the facile formation of the desired sulfamidate products **43–49** (Table 3) in comparable efficiency and selectivity as was observed previously with **1**.



Scheme 2. Synthesis of the novel variants **39–42** of the original Burgess reagent: a) chlorosulfonyl isocyanate (**34**, 1.0 equiv), ROH (1.05 equiv), CH₂Cl₂, 0 °C, 30 min, 89–95%; b) Et₃N (2.5 equiv), C₆H₆, 25 °C, 1 h, 81–87%.

Table 3. Use of the new Burgess-type reagents **39–42** to prepare orthogonally protected sulfamidates **43–49**.

Entry	Starting material	Major product	Ratio of regioisomers ^[a]	Yield [%]
1			> 98:2	90
2			95:5	81
3			> 98:2	87
4			> 98:2	82
5			> 98:2	89
6			> 98:2	87
7			> 98:2	78

[a] Determined by means of ¹H NMR spectroscopic analysis of the crude reaction products. Cbz = CO₂CH₂Ph, Alloc = CO₂CH₂CH=CH₂, Troc = CO₂CH₂CCl₃.

Significantly, preliminary handling of **39–42** suggests that they possess unique thermal and moisture-sensitivity profiles relative to **1**, physical features which could prove significant in transformations that are typically effected by Burgess reagent on recalcitrant substrates. The ability of **39–42** to perform reactions already known with **1**, such as oxazole formation from precursor ketoamides,^[19] is being explored.

Finally, we sought to convert the sulfamidate products into β -amino alcohols. Although this conversion had been disclosed previously in the literature (1:1 mixture of HCl (aq.)/dioxane, ambient temperature), only one substrate was examined.^[9k] To verify that this deprotection protocol had sufficient scope for general synthetic utility, several sulfamidates were readily deprotected under these conditions (Table 4). High yields were observed in all examples, despite relatively large variations in the reaction time necessary for complete conversion.^[20]

Table 4. Deprotection of cyclic sulfamidates using aqueous HCl in dioxane at ambient temperature to yield β -amino alcohols.

Entry	Starting Material	Product	<i>t</i> [h]	Yield [%]
1			10	94
2			30	95
3			12	92
4			2	92
5			26	95
6			24	93
7			16	90

To summarize, a novel regio- and stereoselective two-stage synthesis of β -amino alcohols has been achieved in which the key transformation is the creation of a cyclic sulfamidate from a precursor diol, mediated by Burgess-type reagents. The generality and scope of this approach is underscored by the considerable number and variety of substrates which display high levels of selectivity in the process. As such, this method provides facile access to compounds for use in a myriad of applications, whether as chiral ligands to perform asymmetric synthesis or as molecular probes to explore problems in chemical biology. Further extensions of the utility of the

disclosed sulfamidate synthesis, as well as a full exploration into the physical properties and chemical reactivity of the newly disclosed Burgess-type reagents **39–42**, are the subject of present investigations.

Experimental Section

General procedure: the diol (0.5 mmol, 1.0 equiv) was dissolved in anhydrous THF (5 mL) and **1** (0.293 g, 1.25 mmol, 2.5 equiv) was added. The resultant solution was heated at reflux for 1 h, cooled to ambient temperature, concentrated, and then purified by chromatography on silica gel to afford the desired product in high purity.

Note: although analysis by thin-layer chromatography (TLC) indicates complete consumption of starting materials after a few minutes, uncyclized material **II** (Scheme 1) remains at the baseline, and further heating is required to effect complete conversion into **III**.

Deprotection of the sulfamidate group: the substrate was dissolved in a mixture of HCl (4 M, aq.)/dioxane (1:1) and the solution was stirred at ambient temperature until complete conversion was observed by TLC. The reaction mixture was then diluted with EtOAc, washed with aqueous NaHCO₃ (5 %) and brine, dried over MgSO₄, and concentrated to afford spectroscopically pure **IV**.

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A Supramolecular Array of Fullerenes by Quadruple Hydrogen Bonding**

Luis Sánchez, Minze T. Rispens, and Jan C. Hummelen*

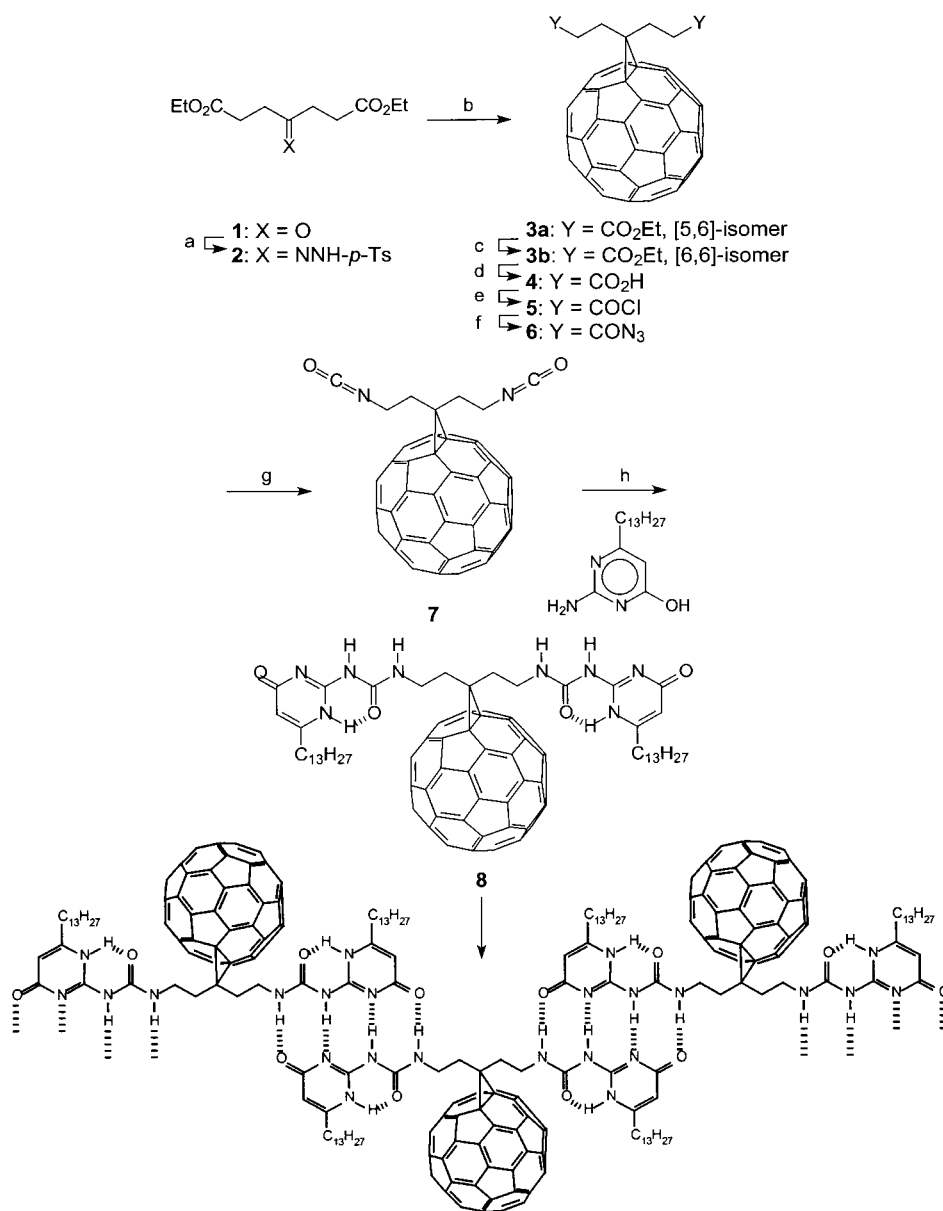
Fullerenes have interesting properties that may be utilized in a variety of applications including organic photovoltaic (PV) devices.^[1] Especially organic bulk-heterojunction PV cells consisting of a blend of a π -conjugated polymer and a fullerene derivative^[2] have received much attention recently. A way to improve the efficiency of these so called “plastic” solar cells is the optimization of the morphology of the photoactive layer. A potential way to attain this goal is through supramolecular assembly of the constituents. Hydrogen bonding is particularly useful in the construction of supramolecular structures.^[3] Relatively little work on C₆₀-based polymers^[4] and supramolecular C₆₀ derivatives has been performed.^[5] So far, only dimeric compounds have been obtained by a supramolecular approach.^[6] Monofunctionalized C₆₀ derivatives bearing one or two hydrogen-bonding moieties on the substituent can serve as building blocks for the preparation of fullerene-containing dimers and arrays, by using the strength, directionality, and specificity, characteristic of hydrogen bonding.^[3] Our group^[7] and the group of Martín^[8] have recently reported on the synthesis of supramolecular C₆₀ dimers bearing Meijer’s self-complementary 2-ureido-4-pyrimidinones which have a donor donor acceptor acceptor (DDAA) hydrogen bonding motif. This motif gives rise to a very high dimerization constant ($K_d \geq 6 \times 10^7 \text{ M}^{-1}$), as a result of attractive secondary interactions.^[9] The presence of two ureidopyrimidinone groups in a molecule results in supramolecular polymers of exceptional properties.^[10] After our first exercise on a fullerene with *one* coupling unit,^[7] we now report the synthesis and spectroscopic characterization of the first hydrogen-bonded supramolecular array, formed by a (methano)fullerene with *two* coupling units.

The synthesis of target monomer **8** (Scheme 1) started with the conversion of diethyl-4-oxopimelate (**1**) into *para*-tosylhydrazide **2**. Heating the anion of **2** in the presence of C₆₀ in 1,2-*ortho*-dichlorobenzene (ODCB) at 100 °C^[11] gave fulleroid **3a**, together with methanofullerene **3b**, higher adducts, and C₆₀, through the intermediate diazo compound and diazoline adduct. The isomeric mixture **3a/3b** was isolated and photoisomerized quantitatively to the [6,6]-isomer **3b**. Hydrolysis of **3b** yielded acid **4**, which was fully characterized despite its insolubility in all common solvents. Target methanofullerene **8** was prepared using a one-pot procedure:

[*] Prof. Dr. J. C. Hummelen, Dr. L. Sánchez, Dr. M. T. Rispens
Stratingh Institute and Materials Science Centre
University of Groningen
Nijenborgh 4, 9747 AG Groningen (The Netherlands)
Fax: (+31) 50-3634296
E-mail: J.C.Hummelen@chem.rug.nl

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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. Synthesis of methanofullerene **8**. a) *p*-TsNHNH₂, EtOH, overnight, Δ , 85 %; b) NaOMe, py, 30 min, RT; then C₆₀ in ODCB, 80 °C, 16 h; c) ODCB, 500 W flood lamp, RT, overnight, 49 % (b,c); d) ODCB, AcOH, HCl, H₂O, Δ , overnight, 83 %; e) SOCl₂, 1 h; f + g) NaN₃, ODCB, Me₂NCOMe, 75 °C, 30 min; h) 2-amino-4-hydroxy-6-tridecylpyrimidine, py, 100 °C, overnight, 43 % (e–h); Ts = tosyl, py = pyridene, Ac = acetyl.

carboxylic acid **4** was converted into acid chloride **5**, after which reaction with sodium azide yielded acyl azide **6**. Heating **6** in the presence of 6-tridecylisocytosine at 100 °C overnight afforded **8** in good yield (43 %, four steps, starting from **4**) via bisocyanate **7**. Full experimental details are in the Supporting Information.

The ¹H NMR spectrum of a relatively concentrated (100 mM) sample of remarkably soluble (oligo and polymeric) target compound **8** in CDCl₃ showed the typical resonances for the six (polymeric) hydrogen-bonding protons at δ = 12.87 (intramolecular, 2H) and at δ = 11.63 and δ = 10.65 (intermolecular, 4H) as well as at δ = 5.72 for the vinylic proton (2H) (Figure 1 a). Disrupting all **8**-to-**8** hydrogen bonding by the addition of a small amount of [D₁]trifluoroacetic acid

(TFA) resulted in converging of all the resonances from the hydrogen-bonding protons at δ = 11.33. The hydrogen-bonded array can be fully restored, as witnessed by the recovery of the original NMR spectrum by precipitation of the TFA-disrupted polymer with methanol, drying, and subsequent dissolving in CDCl₃.

The dynamic behavior of the supramolecular polymer was investigated by ¹H NMR spectroscopy by lowering the concentration to 10 mM in CDCl₃ (Figure 1 b). In addition to all the resonances corresponding to the hydrogen-bonded and vinylic protons observed at 100 mM, new sets of multiple signals appeared. This behavior can be explained by the existence of oligo- and polymeric aggregates in the concentrated solution and a mixture of polymeric and low molecular weight cyclic aggregates in the diluted solution, and is in full agreement with earlier results on supramolecular polymers held together by this coupling unit.^[9, 10, 12] Theoretically, based on an association constant of $6 \times 10^7 \text{ M}^{-1}$ in CHCl₃,^[9] the population of associates of ultra pure **8** at 100 mM is expected to peak at a M_n of $\approx 3.6 \times 10^6$. In reality, however, the effect of tiny amounts of (monofunctional) impurities substantially lowering the dynamic molecular weight distribution has to be taken into account.

Further support for the polymeric nature of **8** at high concentration was obtained upon investigating the processability and thin-film behavior of **8**: When a filtered solution of **8** (10 mM in CHCl₃) was spin-coated on a glass

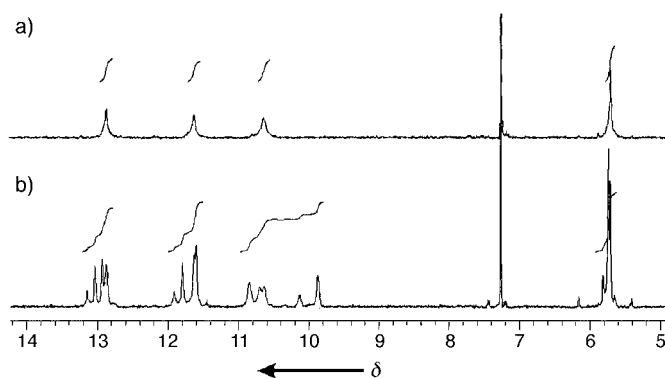


Figure 1. ¹H NMR spectra of compound **8** in CDCl₃ at different concentrations, a) 100 mM and b) 10 mM.

substrate, a macroscopically homogeneous film was obtained in contrast to the behavior of many low molecular weight fullerene materials. Upon spin-coating, the concentration of **8** increases dramatically, instantly generating higher molecular weight polymer. The UV/Vis spectrum of the film showed substantial scattering, but subtraction of a weighted $1/\lambda^4$ curve regenerated the solution spectrum, albeit somewhat red shifted in the 500–550 nm region. This behavior resembles that of C_{60} in solution and solid-state spectra.^[13]

The ^{13}C NMR spectrum of polymeric **8** (at 100 mm in CDCl_3) showed 15 signals for the fullerene core in accordance with a C_{2v} symmetry for the monomer. Additional resonances at $\delta = 172.87$, 156.63, 154.10, and 152.33, which correspond to the 2-ureido-4-pyrimidinone moiety, and at $\delta = 78.21$ and 39.92, diagnostic for the cyclopropyl moiety, were observed. The UV/Vis of **8** revealed the characteristic absorptions for a methanofullerene. There were no significant spectral shifts in the 400–750 nm region upon varying the concentration between 0.01 and 4 mM, which indicates little or no ground-state interfullerene interaction in the “supra polymer”. The FT infrared (IR) spectrum of **8** (KBr pellet) showed the typical peak pattern for a 4[1H]-ureidopyrimidinone derivative (1697, 1656, 1585, 1524 cm^{-1}) together with a peak at 526 cm^{-1} , diagnostic for a (monomethano)fullerene. Finally, in the matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrum of **8** a parent peak at m/z 1457.79 was detected, which corresponds to the monomer formula. No higher aggregates were observed.

The redox behavior of **8** (at 0.3 mM in ODCB:MeCN 4:1) was studied by cyclic voltammetry (Figure 2). Four quasi-reversible fullerene-core reduction waves were observed, with values typical for this type of methanofullerene.^[7] A small wave at -1.79 V, which corresponds to the reduction of the ureidopyrimidinone moiety was also observed. In the dimer, this moiety showed two reduction waves at -1.15 (sh) and -1.84 V.^[7] In **8** only the latter can be distinguished, probably because of overlapping of the first with the second reduction wave of the fullerene moiety, as indicated by the increased size of the 2nd reduction wave, compared to the first. The presence of a clean set of waves indicates that there is little or no interaction between the fullerene cages, in agreement with the redox behavior determined for the corresponding supramolecular dimers (Figure 2).^[7]

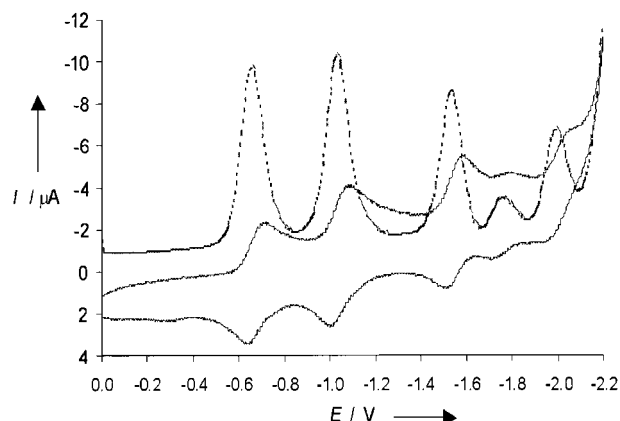


Figure 2. Cyclic (—) and differential-pulse voltammograms (---) of compound **8**.

Polymer **8** is first example of a hydrogen-bonded fullerene array. In the highly dynamic polymeric state, the chemical integrity of the monomeric moiety is fully preserved, also with respect to its redox and UV/Vis behavior. Application in supramolecular electronics, for example, in combination with (supra)molecular donor materials, is now underway.

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Callipeltoside A: Assignment of Absolute and Relative Configuration by Total Synthesis**

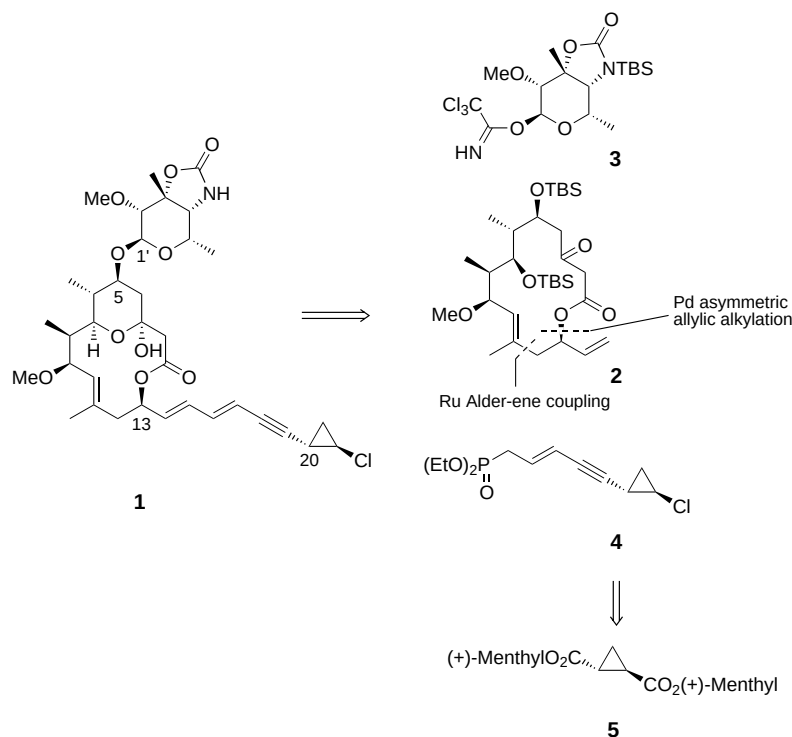
Barry M. Trost,* Olivier Dirat, and Janet L. Gunzner

Callipeltoside A (**1**) was isolated by Minale and co-workers in 1996 from the shallow water sponge *callipelta* sp., collected off the east coast of New Caledonia.^[1] This new macrolide was found to inhibit the proliferation of NSCLC-L6 human bronchopulmonary nonsmall-cell-lung carcinoma (11.26 $\mu\text{g mL}^{-1}$) and P388 (15.26 $\mu\text{g mL}^{-1}$) cells in vitro.^[1a] The small amount (3.5 mg) of **1** obtained led to the determination of its structure by extensive NMR spectroscopic studies. The relative stereochemical relationship of callipeltose to the macrolactone has been assigned based on two NOE interactions—an assignment supported by our recent total synthesis of deschlorocallipeltoside A.^[1a, 2] Two main stereochemical issues remain unsolved: a) the absolute configuration, and b) the relative configuration of the *trans* chlorocyclopropane with regard to the macrolactone. Indeed, the isolation of the chlorocyclopropane from the rest of the molecule provides no detectable bias by NMR spectroscopy, as shown by the synthesis of two diastereoisomers of the aglycon of callipeltoside A by Paterson et al.^[3] In spite of these structural ambiguities, many groups have embarked on the total synthesis of the compound, with different stereoisomers as targets.^[4] We report the unambiguous assignment of the absolute and relative configuration of callipeltoside A by means of the total synthesis of several stereoisomers.

Our choice for the absolute configuration of the macrolactone that we synthesized has been dictated by analogy with a structurally similar molecule, auriside B. The absolute configuration of this marine macrolide has been determined by degradation studies, and its sugar moiety matches L-rhamnose.^[5] Therefore, we chose L-rhamnose as starting material for the sugar synthesis. To the extent that the NOE correlation in the original structural determination is valid, the absolute configuration of the macrolactone then is also indicated. We based our strategy on our recent

total synthesis of deschlorocallipeltoside A, in which the macrolactone **2** was obtained in 16 linear steps, highlighted by a ruthenium-catalyzed Alder-ene alkene–alkyne coupling, followed by a palladium-catalyzed asymmetric allylic alkylation to set the C13 stereocenter. The trichloroimidate **3** was obtained in 14 steps from L-rhamnose.^[2]

Our convergent approach is illustrated in Scheme 1.^[6] Callipeltoside A comes from a late-stage coupling of the side



Scheme 1. Retrosynthesis of callipeltoside A (**1**). TBS = *tert*-butyldimethylsilyl.

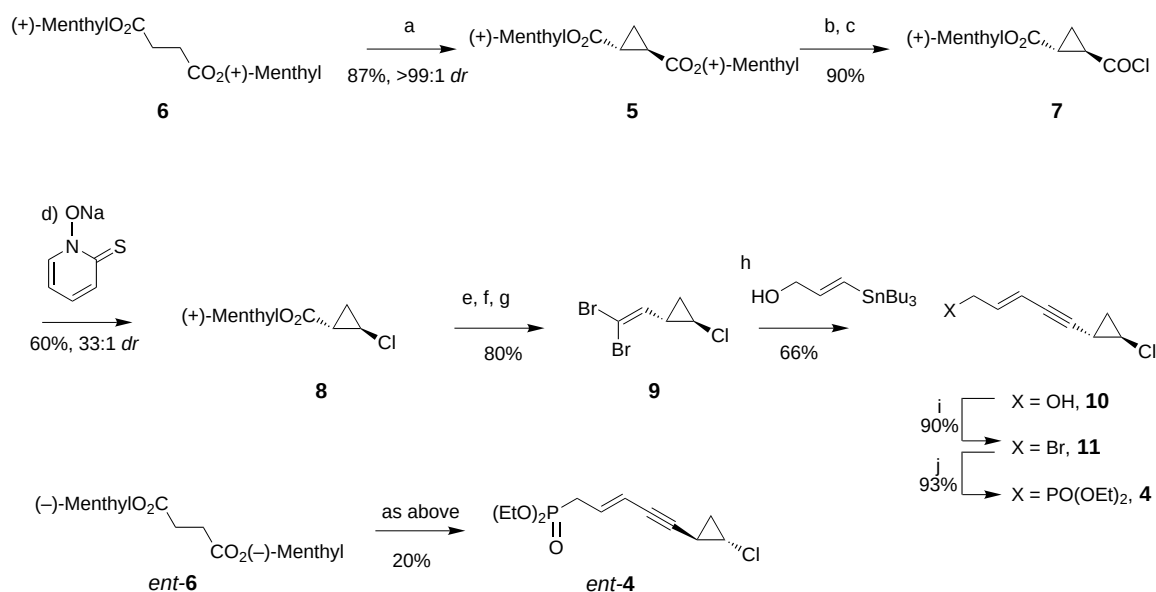
chain by an Emmons–Wadsworth–Horner olefination, followed by a Schmidt glycosidation. The synthesis of the side chain **4** takes advantage of the modified Stille reaction described by Shen^[8a] to form internal alkynes, and uses Yamamoto's method^[8b, c] to access easily multigram quantities of both enantiomers of **5**. Scheme 2 illustrates the synthesis of the side chain **4**, performed for both enantiomers. The synthesis starts from the commercially available (for both enantiomers)^[7] dimethyl succinate (**6**) to form known cyclopropane **5** with almost perfect diastereoselectivity after one recrystallization in methanol.^[8a, b] One of the menthyl esters was transformed into known acid chloride **7** in excellent yield by using a literature procedure.^[9] Acid chloride **7** was transformed into chloride **8** by using the Barton–Crich–Motherwell decarboxylation in carbon tetrachloride.^[10]

A careful study of this reaction proved that, unlike most of the literature precedents, the low-yielding step of this two-step one-pot process is not the formation of the Barton ester, but the radical reaction.^[11] Indeed, the direct radical reaction of the pure Barton ester (prepared from the corresponding carboxylic acid, tributylphosphane, and 2,2'-dithiobis(pyridine-*N*-oxide)^[11a]) in the same conditions, gave similar yields to the two-step process (ca. 60 %). Our optimized conditions

[*] Prof. B. M. Trost, Dr. O. Dirat, Dr. J. L. Gunzner
Department of Chemistry, Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-723-3385
E-mail: bmtrost@stanford.edu

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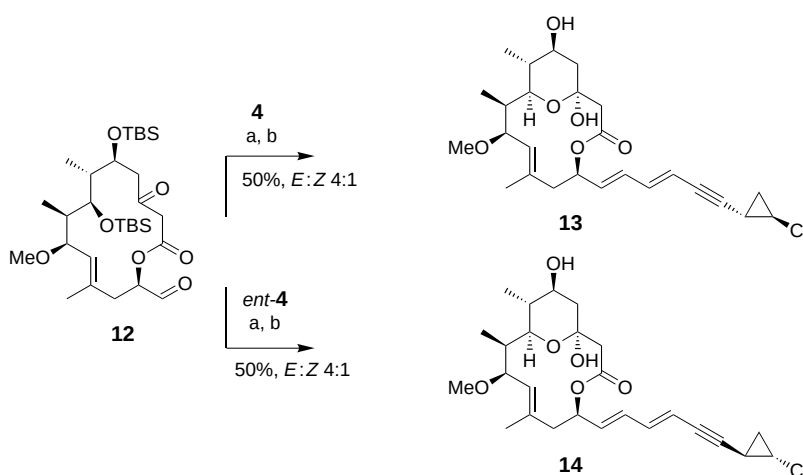
Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 2. Synthesis of the side chain. a) LiTMP, BrCH₂Cl, THF, −78 °C. b) NaOH (5 M), *i*PrOH, 70 °C. c) SOCl₂, room temperature. d) DMAP, *n*Bu₄NI, CCl₄ (0.02 M), 1 h, room temperature, then AIBN, 5 h, 80 °C. e) CH₃NHOCH₃ · HCl, *i*PrMgCl, THF, −10 °C. f) DIBALH, CH₂Cl₂, −78 °C. g) CBr₄, PPh₃, CH₂Cl₂, room temperature. h) [Pd₂(dba)₃] · CHCl₃, (4-CH₃OPh)₃P, DIPEA, DMF, 80 °C. i) CBr₄, PPh₃, CH₂Cl₂, −40 °C. j) P(OC₂H₅)₃, 100 °C. LiTMP = lithium 2,2,6,6-tetramethylpiperidine, DMAP = 4-dimethylaminopyridine, AIBN = azobisisobutyronitrile, DIBALH = diisobutylaluminum hydride, DIPEA = diisopropylethylamine, dba = *trans,trans*-dibenzylideneacetone.

yielded *trans*-chlorocyclopropane **8** in a reproducible 60% yield (9 mmol scale, 33:1 diastereomeric ratio).^[12] This reaction can be performed in 10 min (instead of 6 h) under microwave^[13] irradiation (150 °C) in 52% yield, and needs to be performed under dilute conditions (0.02 M). Chloride **8** was then converted in three steps into known dibromoolefin **9**^[4c,d] via a Weinreb amide in excellent yield.^[14, 15] We then used the Stille conditions developed by Shen and used by Olivo for this reaction to produce known enyne **10**^[4c,d] in moderate yield. Enne **10** is easily transformed into phosphonate **4** via the corresponding bromide **11** in good yield.^[8a, 16] The side chain **4** was synthesized over ten linear steps from the commercially available dimethyl succinate in an overall yield of 20%. By using the enantiomeric starting succinate ester, *ent*-**4** was obtained in similar overall yield.

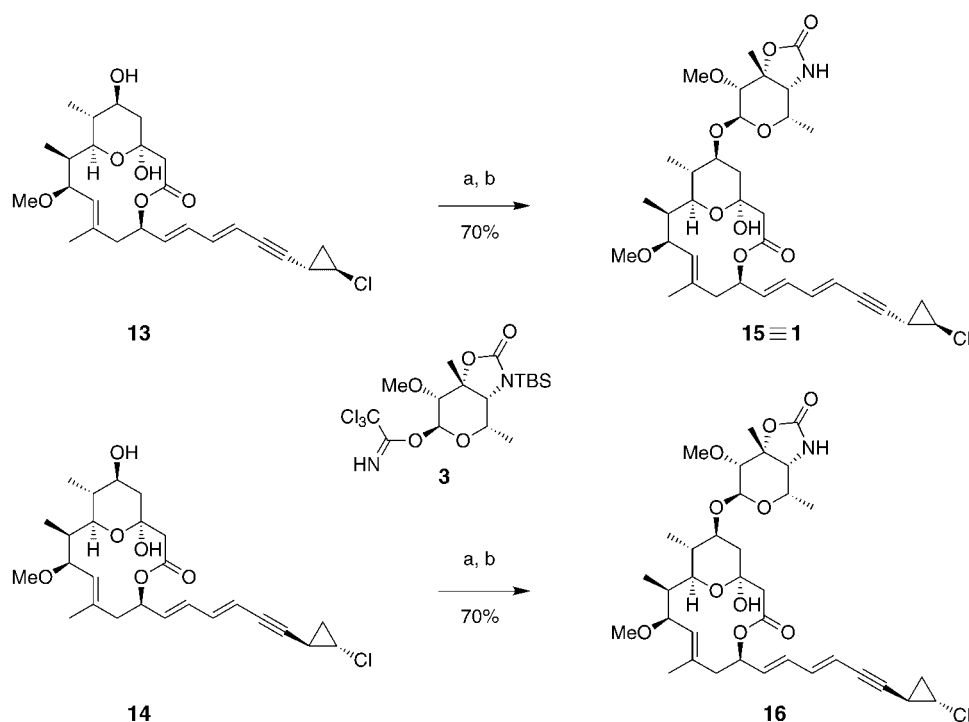
The side chains **4** and *ent*-**4** were coupled to macrolactone **12** by using an Emmons–Wadsworth–Horner,^[2] and proceeded in modest yields (52%; *E*:*Z* 4:1). The callipeltoside A aglycons **13** (prepared from **4**) and **14** (prepared from *ent*-**4**) were obtained in 96% yield after deprotection with HF · pyridine in methanol (Scheme 3).^[17] Comparison of the analytical data of our synthetic aglycons with those of the enantiomeric aglycons reported by Paterson et al. shows a perfect match.^[18] The glycosidation and final deprotection gave a single diastereoisomer. Two diastereoisomers of callipeltoside A, **15** (prepared from **4**) and **16** (prepared from *ent*-**4**), have been synthesized in a 22-step longest linear sequence, and 50 total steps in 0.47% overall yield. The ¹H and ¹³C NMR spectroscopic data shows, as expected, no difference between **15**, **16**, and the natural sample (Scheme 4).^[19]



Scheme 3. Synthesis of the callipeltoside aglycons. a) LiHMDS, THF, −78 °C, then −40 °C, then room temperature; b) HF · pyridine, MeOH, 0 °C. LiHMDS = lithium

The unambiguous assignment of the absolute and relative configuration comes from the rotation values. Indeed, **15** has a rotation of $[\alpha]_D^{25} = -19.2$ ($c = 1.0$, CH₃OH), very close in absolute value to and with the same sign as the natural sample $[\alpha]_D = -17.6$ ($c = 0.04$, CH₃OH), whereas **16** has a rotation of $[\alpha]_D^{25} = +156.3$ ($c = 0.55$, CH₃OH). This significant difference allows us to assign the absolute and relative configuration of callipeltoside A (**1**) as **15**.

This synthesis of callipeltoside A (**1**) is highly convergent: the three main pieces of the molecule, that is, the macrolactone, the side chain, and the sugar, are assembled within the last four steps of the synthesis. This convergent approach is perfectly suited to pursue structure–activity studies, and enabled us to synthesize two isomers of **1**. The synthesis of the



Scheme 4. Completion of the synthesis. a) **3**, TMSOTf, 4-Å molecular sieves, 1,2-dichloroethane, -30°C . b) TBAF, AcOH, THF, room temperature. TMSOTf = trimethylsilyl trifluoromethanesulfonate, TBAF = tetrabutylammonium fluoride.

analogues as well as their biological evaluation is underway and will be reported in due course.

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- [12] The first step of the process is performed at room temperature in the dark in the presence of a phase-transfer catalyst to facilitate the formation of the Barton ester. The second step of the process is performed at reflux in the presence of light and a radical initiator to favor the radical chain over thermal degradation.
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- [16] All spectroscopic data, with the exception of the rotation of **10/ent-10**, are identical to those reported (ref. [4d]); rotation of **10**: $[\alpha]_D^{25} = -222.7$ ($c = 0.70$, CH_2Cl_2); rotation of **ent-10**: $[\alpha]_D^{25} = +225.5$ ($c = 0.70$, CH_2Cl_2), literature value (ref. [4d]): $[\alpha]_D^{25} = -78.9$ ($c = 0.705$, CH_2Cl_2).
- [17] The transketalization (pyridinium *p*-toluenesulfonate, MeCN, H_2O) used in our synthesis of deschlorocallipeltoside A was not necessary upon modification of the workup conditions, that is, adding a solution of sodium bicarbonate to the reaction mixture instead of adding the reaction mixture to a solution of sodium bicarbonate.
- [18] For ^1H and ^{13}C NMR spectra of **13** and **14**, see: Supporting Information; rotation of **13**: $[\alpha]_D^{25} = -39.4$ ($c = 1.00$, CHCl_3), to be compared with the reported value for **ent-13** (ref. [3]): $[\alpha]_D^{25} = +45.8$ ($c = 0.28$, CHCl_3); rotation of **14**: $[\alpha]_D^{25} = +125.0$ ($c = 1.00$, CHCl_3), to be compared with the reported value for **ent-14** (ref. [3]): $[\alpha]_D^{25} = -97.8$ ($c = 0.19$, CHCl_3).
- [19] For ^1H and ^{13}C NMR spectra of **15** and **16**, see Supporting Information.

Gallium Flux Synthesis of $\text{Tb}_{3-x}\text{C}_2\text{Si}_8(\text{B}_{12})_3$: A Novel Quaternary Boron-Rich Phase Containing B_{12} Icosahedra**

James R. Salvador, Daniel Bilc, S. D. Mahanti, and
Mercouri G. Kanatzidis*

Aluminum, gallium, and indium fluxes provide substantial advantages in the exploratory synthesis of a large class of quaternary and ternary silicides and germanides.^[1] We have demonstrated that flux chemistry is a powerful tool for the stabilization of complex aluminide/silicide phases of the type $\text{RE}/\text{Ni}/\text{Si}/\text{Al}$ (RE = rare earth metal).^[2] Complex intermetallics can have useful properties such as exceptionally high melting points, hardness, chemical inertness, and high-temperature thermoelectric energy conversion.^[3, 4] In an attempt to extend this chemistry to the $\text{RE}/\text{Ni}/\text{Si}/\text{B}$ systems, as lighter analogues of the Al-based compounds, we have explored the use of liquid gallium in the synthesis of complex silicon borides. We selected gallium because our studies on $\text{RE}/\text{Ni}/\text{Si}/\text{Ga}$ showed that it was exceptionally difficult to form corresponding quaternary phases,^[5] therefore, competing phases of this type were not expected. We hope to establish a methodology leading to new silicon boride compounds, which today are a relatively unfamiliar class. Liquid Ga may be an ideal solvent for such systems because it has a low melting point of 29.6°C and does not react with silicon or boron, though both are soluble in it, and boron and silicon dissolved in the flux are highly reactive.^[6]

Here we describe the discovery of $\text{Tb}_{1.8}\text{Si}_8\text{C}_2(\text{B}_{12})_3$, which was initially found as a minor product of a reaction between Tb, B, Ni, and Si in a 1:6:1:1 molar ratio, respectively, in a 10-fold molar excess of gallium.^[7] Similar reactions with early rare earth metals, B, Ni, and Si in a 1:6:1:1 ratio with a 10-fold excess of gallium yielded mainly REB_6 , REB_{12} , recrystallized silicon, and $\text{Ni}_5\text{Ga}_3\text{Si}_2$.^[8] The formation of $\text{Tb}_{1.8}\text{Si}_8\text{C}_2(\text{B}_{12})_3$ was surprising, since we started with a quinary system of boron, gallium,

silicon, terbium, and nickel, yet both Ni and Ga were excluded from the final product. Adventitious carbon, presumably present in one of the starting materials, was incorporated into the structure to stabilize the new quaternary boron-rich compound. Quaternary boron-rich systems are quite rare; a thorough search of the literature reveals only $\text{RB}_{22}\text{C}_2\text{N}$ (RE = Y, Ho, Er, Tm, and Lu) and $\text{CrSi}_3(\text{B}_{12})\text{Se}_{12}(\text{B}_2\text{Se}_3)_{1.33}$.^[9] The new compound was initially thought to be a ternary phase. Carbon was determined to be part of the structure only after several failed attempts at a rational synthesis with gallium flux, and close inspection of the bond lengths revealed a $1.695(1) \text{ \AA}$ bond between a "boron atom" and its symmetry equivalent. This is shorter than a typical *endo* or *exo* boron–boron bond, but is quite reasonable for a carbon–carbon bond.^[10, 11] Furthermore a successful high-yield synthesis (ca. 90 %) could be carried out only after carbon was added to the reaction mixture. Analogues with lighter RE atoms could not be synthesized.^[12]

The novel compound $\text{Tb}_{1.8}(\text{B}_{12})_3\text{C}_2\text{Si}_8$ represents a new structure type, shown in Figure 1 a.^[13] There are three salient characteristics of this structure: the B_{12} icosahedral cages, an Si_8 ethane-like cluster, and their mode of connectivity. There are four crystallographically distinct types of boron atoms, all

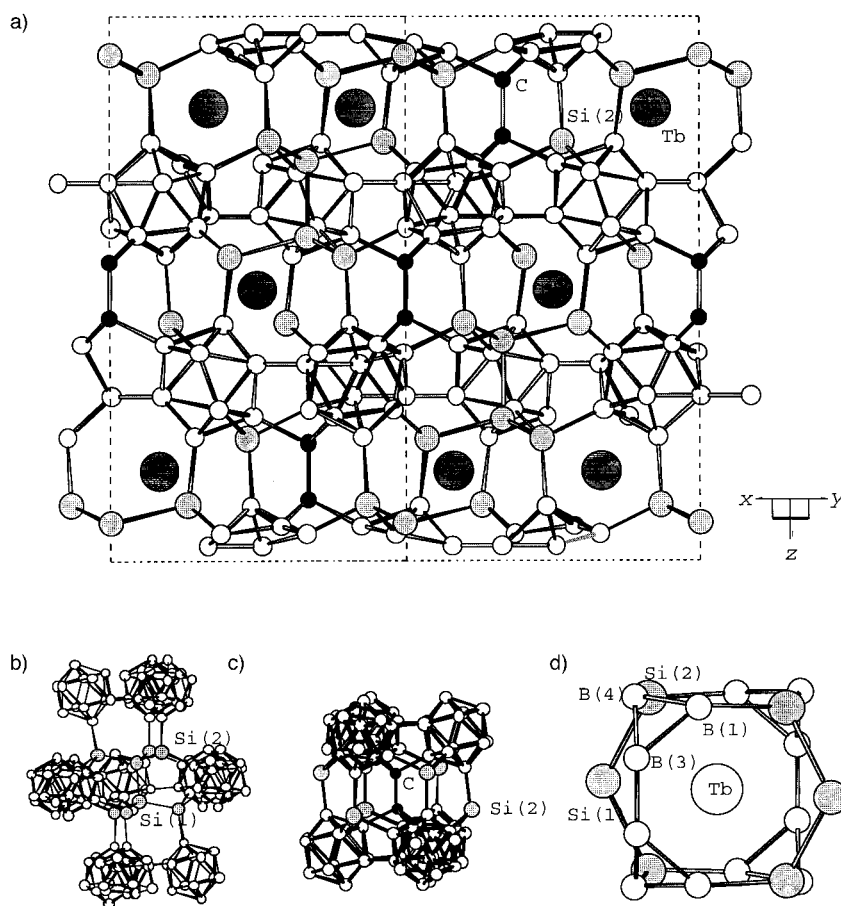


Figure 1. a) View of the unit cell of $\text{Tb}_{3-x}\text{C}_2\text{Si}_8(\text{B}_{12})_3$ showing the boron cage and the connectivity of the Si and C atoms. b) View of the ethane-like Si_8 cluster and its linking motif to the B_{12} cages. c) View of the C–C fragment and its connectivity to the B_{12} units. Shown also is the $\text{Si}(2)$ – B_{12} bonding. d) Coordination environment of the rare earth metal site, caged by Si(1), Si(2), B(1), B(4), and B(3). Tb–B(3) 2.764(4), Tb–B(4) 2.783(4), Tb–Si(2) 2.8391(7) $\text{\AA}$.

[*] Prof. M. G. Kanatzidis, J. R. Salvador

Department of Chemistry
and Center for Fundamental
Materials Research
Michigan State University
East Lansing, MI 4884-1322
(USA)
Fax: (+1) 517-355-1793
E-mail: kanatzid@cem.msu.edu

D. Bilc, Dr. S. D. Mahanti
Department of Physics and Astronomy
Michigan State University
East Lansing, MI 48824-1322 (USA)

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of which are contained in the B_{12} cluster. The B_{12} cluster itself is distorted from ideal geometry and has boron–boron bond lengths of 1.785(7)–1.831(8) Å (av 1.803 Å). This is reasonable for the electron-deficient bonding in the B_{12} icosahedron. The structure contains two crystallographically distinct silicon atoms. The eight Si atoms are clustered together in an ethane-like staggered configuration with a central Si(1)–Si(1) bond length of 2.329(5) Å. Each Si(1) atom is bound to three Si(2) atoms (Si–Si 2.360(2) Å), which in turn form bonds to the B_{12} clusters. The tetrahedral coordination environment of Si(1) is compressed along the Si(1)–Si(1) bond axis, and this results in Si(2)–Si(1)–Si(2) bond angles of 114.25° instead of the ideal tetrahedral angle of 109.5°. The remaining bonds involving Si(2) are to B(1) and B(4) of three separate B_{12} cages (Figure 1b). Each C atom bonds to a symmetry-equivalent atom to give a C–C bond of length 1.695(1) Å in a similarly compressed staggered ethane-like unit with sp^3 hybridization. The carbon atoms form three additional bonds to B(2) of three separate boron cages (B(2)–C 1.820(7) Å, B(2)–C–C 115.5°; Figure 1c).

The B_{12} cage clusters are linked to each other through symmetry generated B(3)–B(3) bonds (1.726(8) Å) and are arranged in a trigonal layer extending over the ab plane (Figure 2). The one crystallographically distinct Tb site refined to 60% occupancy, which is in good agreement with the measured atomic ratios from EDS. The Tb ion is situated on a 3d Wyckoff site and is coordinated by four Si(2) atoms at 2.839(7) Å, two Si(1) atoms at 3.315 Å, and 12 boron atoms at 2.764(4)–2.930(4) Å (Figure 1d).

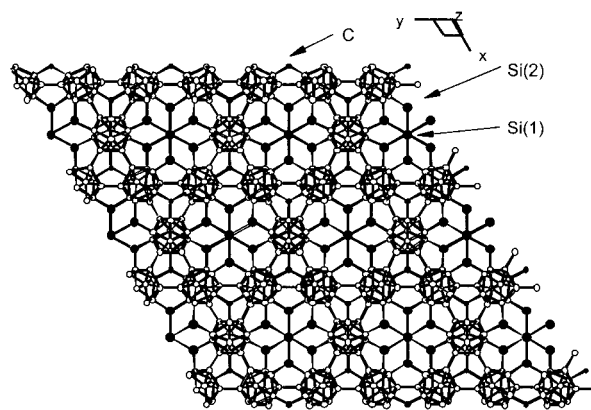


Figure 2. View down the c axis of the layer of B_{12} units and the staggered Si(1)/Si(2) network and their bonding relations. The rare earth metal atoms are omitted for clarity. The B_{12} cages are joined by B(3)–B(3) bonds.

To better understand the origin of the vacancy at the rare earth metal site, an *ab initio* band-structure calculation was carried out.^[14] Due to the difficulty in treating partially filled f levels and vacancies, Tb was modeled by fully occupied La. The resulting band structure and density of states (DOS) suggests that the driving force for the vacancy is valence precision, which consequently establishes a large band gap (ca. 1.0 eV) in the compound (Figure 3a). When the rare earth site is fully occupied, there is nonzero electron density at the Fermi level (i.e., a metal). However, integrating the DOS from –0.5 eV to the Fermi level yields 3.2 electrons, which

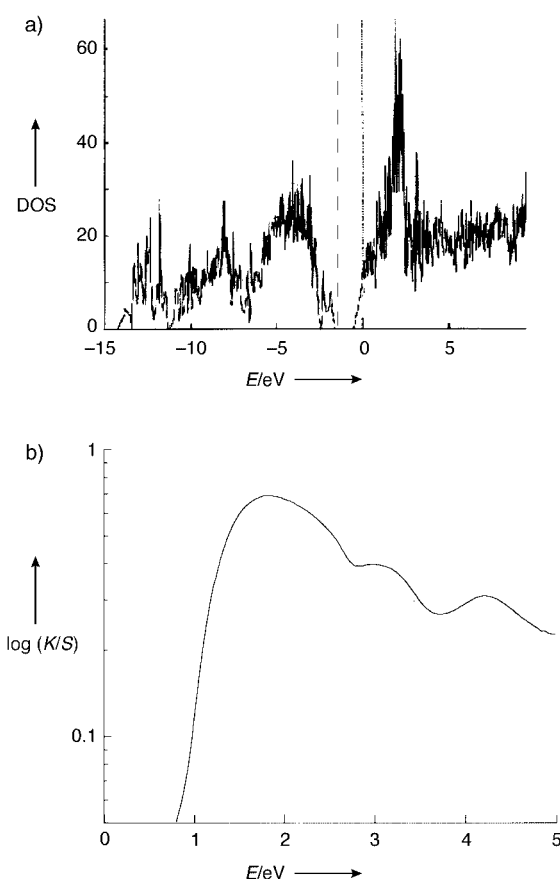


Figure 3. a) Total density of states (DOS) plot for the hypothetical $La_3C_2Si_8(B_{12})_3$. Solid black line is the Fermi level when the rare earth site is fully occupied, and the dotted line is the hypothetical Fermi level for 60% occupancy, which results in a band gap of about 1 eV. b) Experimental optical absorption spectrum of $Tb_3C_2Si_8(B_{12})_3$ showing a band gap of about 0.9 eV.

corresponds well with the removal of approximately 35% of the rare earth metal ions from the compound. The solid line represents the Fermi level with a fully occupied rare earth metal site, and the dotted line is the Fermi level of the species with 65% occupancy. Experimentally we observe 40% removal. The extra 5% may originate from the presence of carbon atoms in the B_{12} cages. This is not unreasonable given the existence of carboranes, and it corresponds to about 5 carbon atoms distributed over 105 boron sites. It is curious that this compound creates vacancies to attain valence precision and a wide band gap, while other compounds such as LaB_6 (the trivalent analogue of the valence-precise compound CaB_6) do not. Instead, the extra electron results in metallic behavior.^[15]

The presence of an optical semiconductor band gap in $Tb_{1.8}(B_{12})_3C_2Si_8$ was confirmed experimentally with near-IR/UV/Vis diffuse reflectance measurements to be about 0.9 eV, in good agreement with the DFT band calculations (Figure 3b).

Magnetic susceptibility measurements were performed on the title compound to establish the oxidation state and the occupancy of the Tb site. Curie–Weiss behavior was observed for the compound down to 20 K, where small deviations indicative of antiferromagnetic interactions were observed.

The calculated effective magnetic moment of $9.60 \mu_B$ per mole of rare earth metal, assuming the site is 60% occupied, is in good agreement with the calculated value of $9.72 \mu_B$.^[16] The Weiss temperature of -17 K is consistent with a small antiferromagnetic interaction of the Tb atoms. The large Tb–Tb distances of 5 Å and the presence of vacancies explain the weak interactions between the Tb sites.

We have demonstrated here the utility of liquid gallium for the synthesis of the novel quaternary boron silicon carbide $Tb_{1.8}Si_8C_2(B_{12})_3$. We also have evidence for isostructural analogues with Y, Sc, Er, Dy, and Tm.^[17] The existence and stability of such complex metal silicide carbide boride compounds should encourage additional exploratory research in this relatively unfamiliar area.

Experimental Section

The optimized synthesis used boron (0.0195 g, 1.80 mmol), amorphous silicon (0.0112 g, 0.4 mmol), graphitic carbon (0.002 g, 0.2 mmol), terbium metal (0.0143 g, 0.09 mmol), and gallium metal (1.5 g, 21 mmol). All reagents were used without further purification and were combined in an alumina tube, which was flame sealed under a vacuum of 7.0×10^{-5} mbar. The reaction mixture was heated to 1000°C over 12 h, held at 1000°C for 96 h, and cooled to 500°C over 60 h. The reaction product was isolated by warm centrifugation to remove excess gallium, and further isolation was effected by 5 M I_2 in dimethylformamide. Total yield after isolation was generally 90% with approximately 95% purity. Unconsumed boron and recrystallized silicon are the main side products. Magnetic measurements were performed on a Quantum Design superconducting quantum interference device (SQUID) with MPMS software. Temperature-dependent measurements were performed at 500 G.

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- [13] Crystal data for $Tb_{1.8}C_2Si_8(B_{12})_3$: $M_r=923.96$; rhombohedral, space group $R\bar{3}m$, $a=10.1171(9)$, $c=16.397(2)$ Å, $V=1453.4(3)$ Å³, $Z=3$, $\rho_{\text{calcd}}=1.583$, $\mu=3.515$ mm⁻¹, $R1/wR=2.69/5.75\%$ for all 417 unique reflections, 7648 total reflections ($R_{\text{int}}=2.81\%$), and 49 parameters. X-ray diffraction data were collected at room temperature on a Bruker SMART CCD diffractometer with graphite-monochromatized $Mo_{K\alpha}$ radiation ($\lambda=0.71073$ Å). The structure was solved by direct methods and refined with the SHELXL suite of programs (G. M. Sheldrick, SHELXL, Structure Determination Programs, Version 5.0, Siemens Analytical X-Ray Instruments Inc., Madison, WI, **1995**). 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-412170.
- [14] Band-structure calculations were performed with the self-consistent full-potential linearized augmented plane-wave method (LAPW) within density functional theory (DFT) with the generalized gradient approximation (GGA) for the exchange and correlation potential. Scalar relativistic corrections were added, and spin–orbit interaction (SOI) was incorporated by using a second variational procedure. The calculations were performed with the WIEN97 program.
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Novel 1,4-Diphosphanes with Imidazolidin-2-one Backbones as Chiral Ligands: Highly Enantioselective Rh-Catalyzed Hydrogenation of Enamides**

Sang-gi Lee,* Yong Jian Zhang, Choong Eui Song, Jae Kyun Lee, and Jung Hoon Choi

Transition metal catalyzed asymmetric hydrogenation is one of the most powerful methods for the synthesis of optically active compounds, and the development of new chiral phosphanes plays a crucial role in this area.^[1, 2] Since Kagan and Dang developed the first C_2 -symmetric 1,4-diphosphane ligand (diop) in the early 1970s,^[3] many diop analogues (**A** and **B** in Figure 1) have been synthesized and

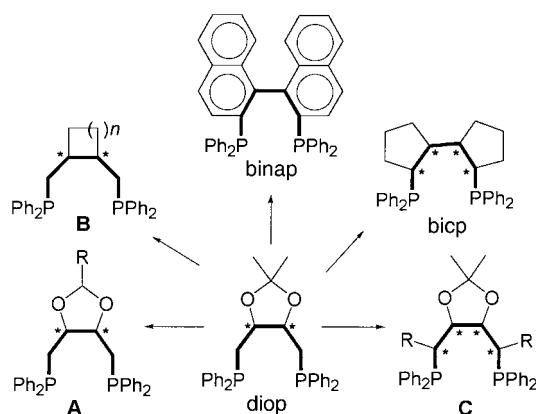


Figure 1. Various types of 1,4-diphosphanes forming seven-membered metal chelate rings.

applied in various asymmetric catalytic reactions.^[4] However, the enantioselectivities obtained with these diop-type 1,4-diphosphane ligands are not always sufficiently high. It is generally believed that the low enantioselectivities with diop-type 1,4-diphosphanes are largely due to the formation of conformationally flexible seven-membered metal-chelate rings. Thus, transfer of backbone chirality through a methylene group to the phenyl group on the phosphane may not be efficient.^[5] Only a few diphosphane ligands forming seven-membered metal chelates (e.g., axially chiral binap^[6] and bicip^[7]) achieved high enantioselectivities. More recently, ligands **C** have been introduced in which the configurations of the stereogenic centers are crucial to obtain high enantio-

selectivity.^[8] Here we report a new type of 1,4-diphosphane ligands with an imidazolidin-2-one backbone, namely, (4*S*,5*S*)-4,5-bis(diphenylphosphanylmethyl)imidazolidin-2-ones **1** (bdpmi, Figure 2), which showed excellent enantioselectivities in Rh-catalyzed hydrogenation of α -arylenamides, a reaction that has attracted considerable attention recently.^[9]

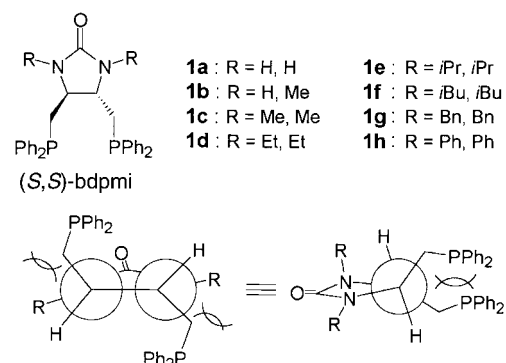
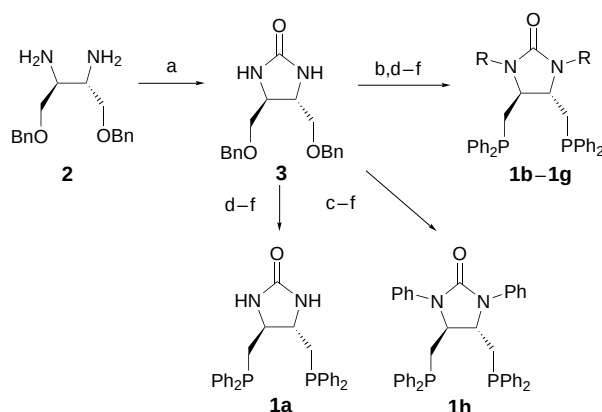


Figure 2. (*S,S*)-bdpmi ligands **1** and the Newman projection showing possible *gauche* interactions.

The design of the bdpmi ligands **1** was based on the following hypothesis: the consecutive *gauche* steric interactions between the N-substituents and phosphanylmethyl groups, as revealed in Newman projections (Figure 2), may influence the conformational flexibility of the seven-membered metal-chelate ring, and the enantioselectivity could therefore be strongly dependent on the steric nature of the R groups.

To test this hypothesis, a number of substituents R with different bulkiness were introduced on the nitrogen atom of imidazolidin-2-one (Scheme 1). Straightforward conversion of L-tartaric acid to the C_2 -symmetric vicinal diamine **2**^[10] and subsequent reaction of **2** with carbonyldiimidazole (CDI) led to the key intermediate **3** in 40% overall yield. Deprotection



Scheme 1. a) CDI (1.2 equiv), CH_2Cl_2 , reflux, 4 h, 94%; b) NaH, RBr, THF, reflux; R = H, Me: 35%; Me, Me: 89%; Et, Et: 91%; *i*Pr, *i*Pr: 16%; *i*Bu, *i*Bu: 43%; Bn, Bn: 90%; c) PhBr, *t*BuONa, Pd-dppf, toluene, 96%; d) $\text{H}_2/\text{Pd}-\text{C}$, MeOH, RT, 82–99% or for R = Bn, Pd(OH)₂/C, cyclohexene, MeOH/EtOAc (1:1), reflux, 81%; e) TsCl (2.2 equiv), pyridine, 71–86% or for R = Bn: MsCl (2.2 equiv), Et₃N, CH_2Cl_2 , 74%; f) KPPH₂, CH_2Cl_2 , RT, R = H, H: 76%; H, Me: 73%; Me, Me: 70%; Et, Et: 67%; *i*Pr, *i*Pr: 74%; *i*Bu, *i*Bu: 77%; Bn, Bn: 74%; Ph, Ph: 70%. dppf = 1,1'-bis(diphenylphosphino)ferrocene.

[*] Dr. S.-g. Lee, Dr. C. E. Song, J. K. Lee
Life Sciences Division
Korea Institute of Science and Technology
P.O. Box 131, Cheongryang, Seoul 130-650 (Korea)
Fax: (+82)2-958-5189
E-mail: sanggi@kist.re.kr
Y. J. Zhang, Prof. J. H. Choi
Department of Chemistry
Hanyang University
Seoul 133-791 (Korea)

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of the *O*-benzyl groups (after *N*-alkylation for **1b–1g**) and tosylation (mesylation for **1g**) followed by reaction with potassium diphenylphosphide afforded ligands **1a–1g**. The *N*-phenyl group of **1h** was introduced by using the Hartwig–Buchwald arylamination method.^[11]

N-Acetylphenylethanamine (**4a**) was used as model substrate for hydrogenation. All reactions were carried out at 20 °C under 1 atm of H₂ and with an Rh:ligand ratio of 1:1.2 (Table 1).^[12] Although a standard reaction time of 12 h was

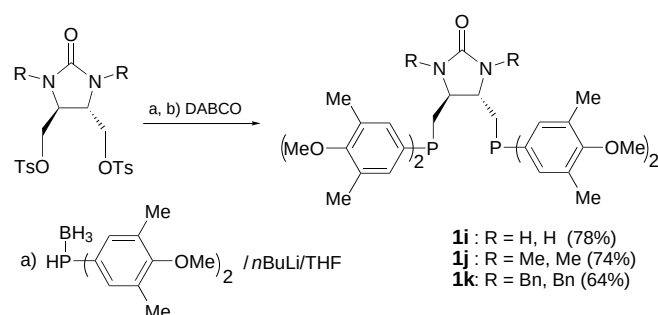
Table 1. Rh-catalyzed asymmetric hydrogenation of *N*-acetyl phenylethanamine **4a** with **1a–1h** as chiral ligands.^[a]

Entry	Ligand	Conv. [%] ^[b]	ee [%] ^[c]	Config. ^[d]
1	(<i>S,S</i>)-diop	100	60.2	<i>R</i>
2	1a	100	86.4	<i>R</i>
3	1b	100	94.0	<i>R</i>
4	1c	100	98.5	<i>R</i>
5	1d	100	97.3	<i>R</i>
6	1e	100	95.7	<i>R</i>
7	1f	100	97.2	<i>R</i>
8	1g	100	96.2	<i>R</i>
9	1h	100	94.6	<i>R</i>

[a] The reaction conditions were [Rh(cod)₂]BF₄:ligand:substrate 0.01:0.012:1, H₂ pressure 1 atm, reaction time 12 h, solvent CH₂Cl₂, room temperature. [b] Determined by ¹H NMR and GC analysis. [c] Determined by chiral GC on a CP-Chirasil-Dex CB column. [d] Determined by comparing the sign of the optical rotation with that reported in ref. [9b].

chosen, most reactions were complete within 4 h. With **1a**, which does not have *N*-substituents, **4a** was hydrogenated to **5a** with 86.4% *ee* (entry 2). Under the same conditions, 60.2% *ee* was obtained with diop (entry 1). Introducing one *N*-methyl group (**1b**) increased the enantioselectivity to 94.0% *ee* (entry 3). The enantioselectivity was further increased with *N,N*-dimethylated ligand **1c** to 98.5% *ee* (entry 4). Comparison of the sense of asymmetric induction imparted by diop, **1a**, **1b**, and **1c** suggested that the steric interactions between the *N*-substituents and the phosphanyl-methyl group is one of the key elements that controls enantioselectivity. However, *N*-substituents larger than methyl resulted in slightly lower enantioselectivities (entries 5–9), that is the *ee* values decreased with increasing *A* values of the *N*-substituents.^[13]

Significantly lower *ee* values were obtained with **1i–1k**, synthesized by reaction of the tosylated intermediates for ligands **1a** and **1c** (mesylated for **1g**) with lithium bis(3,5-dimethyl-4-methoxyphenyl)phosphide–borane complex.^[14] The NH ligand **1i** hydrogenated **4a** with only 40.9% *ee*, whereas the enantioselectivity with the *N,N'*-dimethylated ligand **1j** increased to 86.5% *ee* (Scheme 2). The ligands **1i–1k** possessing electron richer and bulkier phosphane groups uniformly give lower *ee* values than the corresponding **1a**, **1c**, and **1g**, and this indicates that steric effects alone may not be responsible for controlling enantioselectivity. However, the reason for the striking deterioration in enantioselectivity with **1i–1k** is not clear at present.



Scheme 2. Synthesis of ligands **1i–k** and Rh-catalyzed hydrogenation of enamide **4a** with **1i–1k** as ligands. DABCO = 1,4-diazabicyclo[2.2.2]octane.

The catalytic hydrogenation can be applied successfully to a series of α -arylenamides **4b–4g** to give chiral amine derivatives **5b–5g** with Me₂bdpmi **1c** (Table 2). In all cases, the *N,N*-dimethylated ligand **1c** exhibited excellent enantioselectivity. The electronic nature of the *para* substituents in α -phenylenamides has an effect on the enantioselectivity. Enamides with electron-donating substituents (**4b** and **4e**, entries 1 and 4 in Table 2) give higher enantioselectivity than those with electron-withdrawing substituents (**4c** and **4d**, entries 2 and 3). Remarkably, the mixtures of *E*- and *Z*-enamides **4g–4k** (*E/Z* = 1:2.0–2.5) were also reduced with very high enantioselectivities (>99.0% *ee*, entries 6–10). It is noteworthy that the *ee* values of 97.8–99.0% obtained with bdpmi ligand **1c** are higher than or comparable to those obtained with other families of efficient chiral diphosphane ligands.^[8, 9]

Table 2. Rh-catalyzed asymmetric hydrogenation of various *N*-acetyl α -arylenamides with **1c** as chiral ligand.^[a]

Entry	4	Ar, R ¹	Conv. [%] ^[b]	ee [%] ^[c]	Config. ^[d]
1	4b	<i>p</i> -MeC ₆ H ₄ , H	100	98.6	<i>R</i>
2	4c	<i>p</i> -FC ₆ H ₄ , H	100	97.9	<i>R</i>
3	4d	<i>p</i> -ClC ₆ H ₄ , H	100	97.8	<i>R</i>
4	4e	<i>p</i> -MeOC ₆ H ₄ , H	100	99.0	<i>R</i>
5	4f	2-naphthyl, H	100	> 99.0 ^[e]	<i>R</i>
6	4g	C ₆ H ₅ , Me	100	> 99.0	<i>R</i>
7	4h	C ₆ H ₅ , Et	100	> 99.0	<i>R</i>
8	4i	<i>p</i> -MeOC ₆ H ₄ , Me	100	> 99.0	<i>R</i>
9	4j	<i>p</i> -ClC ₆ H ₄ , Me	100	> 99.0	<i>R</i>
10	4k	<i>p</i> -MeC ₆ H ₄ , Me	100	99.0	<i>R</i>

[a] The reaction conditions were [Rh(cod)₂]BF₄:**1c**:substrate 0.01:0.012:1, H₂ pressure 1 atm, reaction time 12 h, solvent CH₂Cl₂, room temperature. [b] Determined by ¹H NMR and GC analysis. [c] Determined by chiral GC on a CP-Chirasil-Dex CB column. [d] Absolute configurations were ascertained by comparison of the sign of optical rotation with that reported in ref. [9b]. [e] Determined by HPLC on a Chiralcel OD column.

In summary, we have developed a new family of 1,4-diphosphanes **1** with an imidazolidin-2-one backbone as chiral ligands and showed their utility in the hydrogenation of α -enamides. The modular construction of this ligand class allows for wide structural diversity. Studies of this kind and mechanistic investigations are underway.

Experimental Section

For details on the synthesis of **1a–1k** and their precursors, see Supporting Information.

General procedure for the asymmetric hydrogenation of enamide **4**: **1** (0.0074 mmol) was added to a solution of [Rh(cod)₂]BF₄ (2.5 mg, 0.0062 mmol; cod = 1,5-cyclooctadiene) in CH₂Cl₂ (2 mL). After the reaction mixture had been stirred at 20 °C for 20 min, enamide **4** (0.62 mmol) was added. The hydrogenation was performed at 20 °C under 1 atm of hydrogen for 12 h. The reaction mixture was passed through a short silica gel column to remove the catalyst. The enantiomeric excess and the reaction conversion were measured by chiral GC or HPLC without any further purification.

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Mimicking Metallophosphatases: Revealing a Role for an OH Group with No Libido**

Marcello Forconi and Nicholas H. Williams*

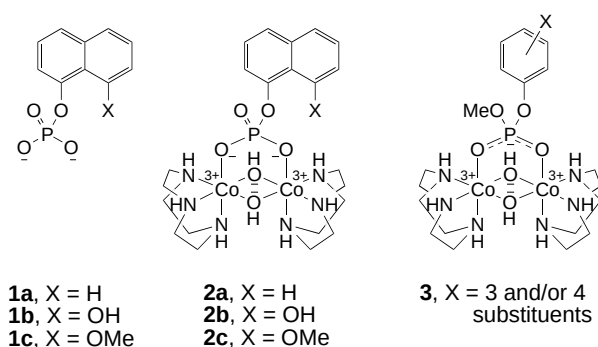
Typically, descriptions of enzyme catalysis use multiple simultaneous interactions between the substrate and the active site to explain the remarkable efficiency which is normally observed.^[1] This poses the intriguing question—do the different interactions operate cooperatively? That is, can a catalytic interaction have a bigger impact when it acts in concert with other complementary interactions than when it is used alone. This is difficult to mimic with simple compounds; usually when multiple interactions are introduced into a model system, it is found that they act independently rather than simultaneously, and such models generally do not rival enzyme efficiency.^[2] Here we report how catalysis of phosphate monoester hydrolysis by an intramolecular OH group becomes much more effective when combined with catalysis by a dinuclear metal ion complex.

We have incorporated phosphate monoesters **1a–c** into dinuclear Co^{III} complexes **2a–c**. We have previously studied this type of complex as a structural and functional model for dinuclear metallophosphatases.^[3] We wanted to investigate the effect of combining intramolecular general acid catalysis with this highly reactive core, as X-ray crystallography has revealed that as well as the metal ions in the active sites of metallophosphatase such as protein phosphatase-1 (PP-1) and kidney bean purple acid phosphatase (KBAP), potential

[*] Dr. N. H. Williams, M. Forconi
Chemistry Department
University of Sheffield
Sheffield S3 7HF (UK)
Fax: (+44)114-2738673
E-mail: N.H.Williams@Sheffield.ac.uk

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general acids are poised to protonate the leaving group.^[4] It has previously been reported that amide hydrolysis promoted by a mononuclear Co^{III} complex can be accelerated an additional 60 fold by an intramolecular phenol in DMSO–water.^[5] Similarly, ammonium groups acting in concert with a Cu^{II} complex provide an additional 1000-fold rate acceleration for phosphate diester hydrolysis in ethanol–water; however, this decreases to <100 fold if the water content is increased to 15%, and would presumably be even less in purely aqueous solution.^[6]

Detailed studies on these complexes with bridging aryl phosphate monoesters^[3, 7] and with bridging methyl aryl diesters (**3**)^[8] show that hydrolysis of the phosphate ester occurs by intramolecular attack of a deprotonated μ -OH group which displaces the aryloxy group. With relatively poor leaving groups, base-catalyzed dissociation of the phosphate group from the complex is also observed in parallel with (or instead of) hydrolysis. Complexes **2a** and **2c** behave just as

expected from these closely related studies. Complex **2a**, whose leaving group has a pK_a of 9.4,^[9] undergoes both base-catalyzed hydrolysis ($k_{HO} = 0.24 \pm 0.01 \text{ M}^{-1} \text{ s}^{-1}$) and dissociation ($k_{HO} = 0.17 \pm 0.01 \text{ M}^{-1} \text{ s}^{-1}$) in a ratio of 59:41. Complex **2c** has a leaving group whose pK_a is 11.4^[10] and thus the ester dissociates from the complex with $k_{HO} = 0.11 \pm 0.01 \text{ M}^{-1} \text{ s}^{-1}$ and without any observable hydrolysis.

³¹P and ¹H NMR spectroscopy show that **2b** predominantly hydrolyzes in wholly aqueous solution to give **4** (Scheme 1) and leave inorganic phosphate bridging the Co^{III} ions in the complex **5**. Interestingly, we also observe that about 5% of the product is cyclic diester **6**. This arises because once deprotonated, the OH group can act as an efficient intramolecular nucleophile, displacing CoO²⁻ from the phosphate (Scheme 1). Once the monodentate diester is formed, this can partition between starting complex and dissociation; we do not observe this species accumulating.

The pH–rate profile (Figure 1) shows that the rate of reaction of **2b** increases with pH until it reaches a plateau

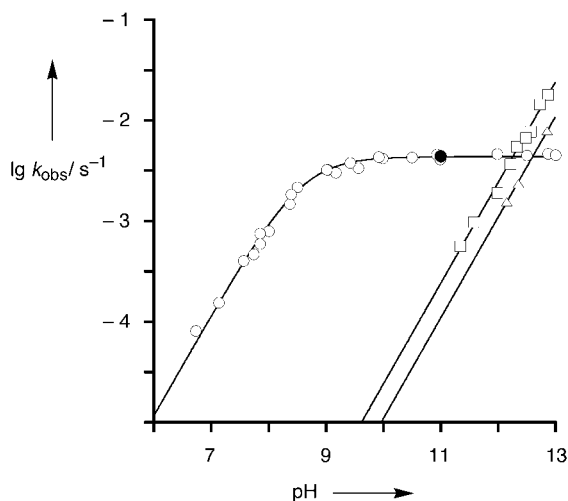
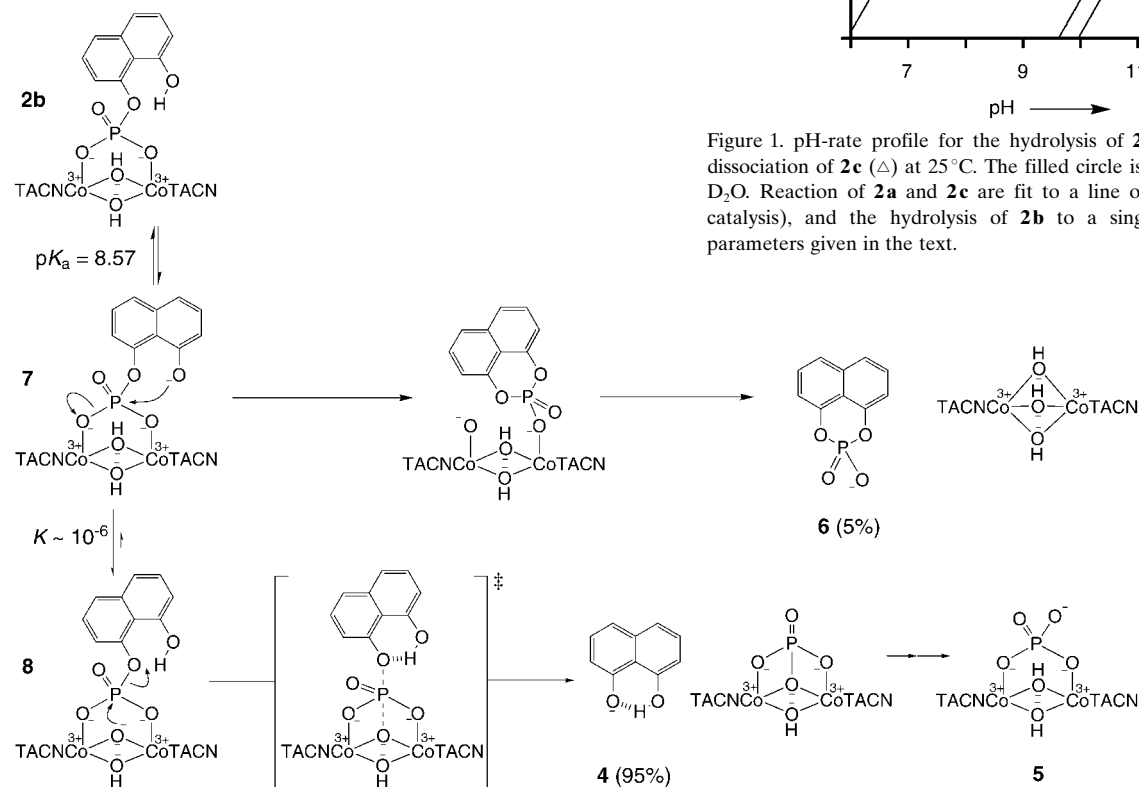


Figure 1. pH–rate profile for the hydrolysis of **2a** (□) and **2b** (○), and dissociation of **2c** (Δ) at 25°C. The filled circle is the hydrolysis of **2b** in D₂O. Reaction of **2a** and **2c** are fit to a line of slope 1 (specific base catalysis), and the hydrolysis of **2b** to a single ionization with the parameters given in the text.



Scheme 1. Proposed mechanism for the reaction of **2b**. TACN = 1,4,7-triazacyclononane.

around pH 9. We assign this pH dependence to the ionization of the ArOH group which means that the observed rate is proportional to the concentration of **7**. Nonlinear least-squares regression gives the pK_a value as 8.57 ± 0.02 , and the plateau rate constant as $0.0044 \pm 0.0001 \text{ s}^{-1}$. Spectroscopic titration of **2b** confirms that the ArOH group has a pK_a of 8.55 ± 0.03 , in excellent agreement with the kinetically determined pK_a value. Based on the mechanism of the closely related aryl phosphate monoester complexes, we propose that hydrolysis proceeds through the (kinetically equivalent) minor tautomer **8** as shown in Scheme 1. Consistent with this interpretation, the solvent isotope effect (at $pD = 11$) is 1.0. Displacement of the naphthalenediol dianion in this pH range is not observed because this is a much poorer leaving group (the pK_a of **4** is > 13 ^[9]).

As the dianion of a phenyl phosphate with a leaving group pK_a value of 9.4 has an estimated rate constant for hydrolysis of $3 \times 10^{-12} \text{ s}^{-1}$ at 39°C ,^[11] the rate on the plateau represents a $> 10^9$ -fold rate acceleration. However, as the pK_a value of the bridging OH group is at least six units higher than the ArOH,^[3] only about 0.0001% of the substrate is in the reactive tautomer in the pH-independent region. This means that the first-order rate constant for the reaction of **8** is about 4000 s^{-1} at 25°C which corresponds to a rate acceleration of approximately 10^{15} fold.

Proton transfer is an essential part of most transformations, and although it is assumed to be efficiently carried out by enzymes it has proved to be a difficult process to model effectively in aqueous solution.^[12] Jencks has suggested that a requirement for general acid catalysis to play a significant catalytic role in solution is the “libido” rule. If the leaving group is less basic than the general acid in the starting material, but becomes more basic in the product, then there is a thermodynamic benefit to catalyzing the reaction by transferring the proton from acid to leaving group in the course of the reaction.^[13] This contributes to effective catalysis without any requirement for special properties of hydrogen bonds in the transition state, as has been the subject of recent debate.^[14] In our complex, the pK_a value of the general acid and the leaving group are identical in the product, so the rule is not obeyed and the intramolecular OH group can only contribute to catalysis by hydrogen-bond formation.

However, within the complex, the OH group accelerates specific base-catalyzed hydrolysis of the monoester very effectively (below pH 8, the reaction is specific base-catalyzed with $k_{\text{HO}} = 1160 \pm 50 \text{ M}^{-1} \text{ s}^{-1}$). Compared to the H analogue **2a**, hydrolysis is accelerated 5000 fold, and compared to the OMe analogue **2c**, more than 50000 fold.

It is possible that the OH group could accelerate attack at the phosphate group by protonating the P=O unit to catalyze the formation of a pentacoordinate intermediate similarly to the suggested “triest-er-like” mechanism for RNA transesterification.^[15] However, we note that in the diester complex **3** which models the reactivity of a fully protonated P=O unit, k_{HO} is approximately $20 \text{ M}^{-1} \text{ s}^{-1}$ ^[8] for a leaving group with a pK_a value of 9.4 which is about 60 fold slower than **2b**. Hence, the OH group is not accelerating the reaction by protonating the P=O unit of the ester. Increasing the steric hindrance near the labile bond also needs to be considered in case this makes

a partial contribution to the overall acceleration. However, we note that in fact **2a** hydrolyzes about fourfold slower than an aryl phosphate complex with a leaving group with the same pK_a value but without substituents in the 2-position,^[3] showing that increasing steric hindrance destabilizes the transition state slightly more than the ground state. Hence, substituents in the 8-position of the 1-naphthol leaving group will inhibit rather than accelerate the rate of reaction.

When the monoester **1b** is not bound to the complex, it is only hydrolyzed tenfold faster than **1c**.^[16] This is consistent with other data which also show that an adjacent OH group of similar pK_a value to the leaving group provides only approximately tenfold rate acceleration (in carboxylic ester hydrolysis^[17] and phosphate triester hydrolysis^[18]). In phosphate monoester dianion hydrolysis in solution, the bond to the leaving group is largely broken, with an estimated charge of -0.88 on the leaving group O atom in the transition state,^[3] and so the scope for the OH group to play a role might be expected to be greatest. Thus, it is particularly striking that the effect of the adjacent hydroxy group is so much greater in this complex. Within complex **2**, the extent of bond cleavage in the transition state is considerably less, giving an estimated charge of -0.36 on the leaving group O atom in the transition state,^[3] but the catalytic effect is much greater.

In conclusion, combining several functional groups to promote phosphate monoester hydrolysis has revealed a large catalytic role for a carefully positioned OH group, even though it doesn't obey the libido rule. In energetic terms, the effect of the adjacent OH group on the transition state (5000-fold rate acceleration $\sim 21 \text{ kJ mol}^{-1}$) is actually greater than in the product anion (the first pK_a of 1,8-naphthalenediol is 6.6,^[9] 2.8 units lower than 1-naphthol $\sim 16 \text{ kJ mol}^{-1}$)^[19] despite only partial charge development at the leaving group.

Experimental Section

The hydrolysis of complexes **2a**, **2b**, and **2c** (0.05 mM) at 25°C in aqueous buffers (50 mM HEPES, EPPS, CHES, or CAPS, $I = 0.1 \text{ M}$ (NaClO_4); or dilute NaOH, $I = 0.1 \text{ M}$ (NaClO_4)) were monitored by following the changes in UV/Vis absorbance using a Cary 1Bio spectrometer with a thermostatted cell holder. Reactions were initiated by the addition of 0.05 mL of a stock solution of the substrate to 3 mL of the buffer which had been equilibrated in the cell compartment for at least 20 min. pH values were measured after each reaction and did not change from the previously measured pH value of each buffer. Isosbestic points and good first-order kinetics for at least three half lives were observed in each case. Pseudo-first-order rate constants were obtained by fitting the change in absorbance (at 317, 341, and 286 nm for **2a**, **2b**, and **2c**, respectively) with time to an exponential function by nonlinear least-squares regression. The products were identified by comparison of the ^1H and ^{31}P NMR spectra with those of authentic samples, and ratios were determined by integration of the ^1H NMR spectra. The pK_a values of 1-naphthol (9.43 ± 0.02) and 1,8-dihydroxynaphthol (6.59 ± 0.04 ; second $pK_a > 13$) were determined by spectroscopic titration at 341 nm under our conditions ($I = 0.1 \text{ M}$ (NaClO_4), 25°C) and correspond with literature values.^[9] The pK_a value of **2b** (8.55 ± 0.03) was determined similarly; in this case, due to the rate of hydrolysis, it was necessary to extrapolate the observed absorbance back to the time of mixing to evaluate the absorbance of **2b** at various pH values. These extrapolations were for $\leq 20 \text{ s}$ and were obtained by using the same first-order exponential curve fitting as for the kinetic measurements over ≥ 5 half lives ($\geq 770 \text{ s}$). Complex **1a** was obtained from Aldrich and used as received. Complexes **1b**, **1c** and **2** were synthesized according to previously reported methods.^[3, 16]

2a: ^1H NMR (250 MHz, D_2O): $\delta = 2.5\text{--}2.75$ (12H, m; CH_2), 3.05–3.35 (12H, m; CH_2), 6.05 (2H, bs; NH), 6.30 (2H, bs; NH), 6.70 (2H, bs; NH), 7.40 (1H, d, $J = 7.82$ Hz; ArH), 7.50 (1H, t, $J = 7.82$ Hz; ArH), 7.58–7.67 (2H, m; ArH), 7.75 (1H, d, $J = 7.82$ Hz; ArH), 7.95–8.03 (1H, m; ArH), 8.22–8.30 (1H, m; ArH); ^{31}P NMR (160 MHz, D_2O): $\delta = 14.1$, ESMS: 831 [MH^+], 731 [$\text{M} - \text{ClO}_4^-$], 631 [$\text{M} - \text{ClO}_4^- - \text{HClO}_4$].

2b: ^1H NMR (400 MHz, D_2O): $\delta = 2.40\text{--}2.65$ (12H, m; CH_2), 2.95–3.15 (12H, m; CH_2), 6.20 (2H, bs; NH), 6.27 (2H, bs; NH), 6.53 (2H, bs; NH), 6.90 (1H, d, $J = 7.70$ Hz; ArH), 7.28 (1H, d, $J = 7.70$ Hz; ArH), 7.30–7.38 (2H, m; ArH), 7.44 (1H, d, $J = 9.30$ Hz; ArH), 7.58 (1H, d, $J = 9.30$ Hz; ArH); ^{31}P NMR (160 MHz, D_2O): $\delta = 13.0$, ESMS: 847 [MH^+], 747 [$\text{M} - \text{ClO}_4^-$], 647 [$\text{M} - \text{ClO}_4^- - \text{HClO}_4$].

2c: ^1H NMR (250 MHz, D_2O): $\delta = 2.5\text{--}2.75$ (12H, m; CH_2), 3.05–3.35 (12H, m; CH_2), 3.95 (3H, s; OMe), 6.20 (2H, bs; NH), 6.60 (2H, bs; NH), 6.85 (2H, bs; NH), 7.08 (1H, d, $J = 7.70$ Hz; ArH), 7.33 (1H, d, $J = 7.70$ Hz; ArH), 7.42–7.60 (3H, m; ArH), 7.75 (1H, d, $J = 9.30$ Hz; ArH); ^{31}P NMR (160 MHz, D_2O): $\delta = 11.9$.

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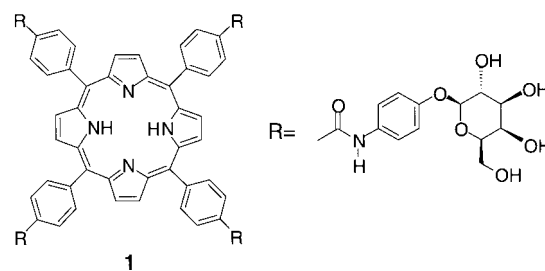
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Sol–Gel Transcription of Sugar-Appended Porphyrin Assemblies into Fibrous Silica: Unimolecular Stacks versus Helical Bundles as Templates

Shun-ichi Tamaru, Masayuki Takeuchi, Masahito Sano, and Seiji Shinkai*

A diverse range of supramolecular structures can be created, not only in nature but also in an artificial system, by self-assembly of designed organic building blocks. In general, the creation of such diverse supramolecular structures seems to be very difficult or nearly impossible in inorganic materials. Is there any innovative method by which ordered supramolecular structures can be created from inorganic materials? The sole method is to transcribe the supramolecular structures of organic molecular assemblies into inorganic materials. It is known that amphiphilic organic molecules are self-assembled into various supramolecular structures,^[1] which can be utilized as templates to create novel mesophasic inorganic materials in mesoporous materials,^[2] vesicles,^[3] ultrathin membranes,^[4] etc.^[5] As natural examples of these processes, one can prepare inorganic microfibers by mineralization of bacterial fibers^[6] or of self-assembled lipid tubules of a galactocerebroside and a phosphate.^[7] Since in these attempts it is very important to “design” the different size and shape of the inorganic materials (in the same way that organic compounds and assemblies are “designed”), it has been desirable to explore the use of various organic materials as templates and elucidate the mechanism of the template effect.^[8] Thus, it is now possible to “design” the inorganic catalysts, electrode devices, etc. at a micrometer level.^[9]

Increasing attention has been paid to low molecular mass compounds that can efficiently gelate various organic solvents.^[10–21] These phenomena are interesting in that the fibrous aggregates formed by noncovalent interactions are responsible for the gelation. We have shown that these “organic” superstructures can be elaborately transcribed into “inorganic” silica materials by utilizing template–silanol interactions.^[22] Recently, we found that an amphiphilic porphyrin (**1**) bearing four β -D-galactopyranoside groups at its periphery tends to aggregate in a one-dimensional direction, which results in very robust gels in DMF/alcohol mixed solvents.^[23, 24] Interestingly, we noticed that the speed of bundle growth of this gelator is relatively slow, which would provide us with a greater chance to transcribe nanosized



incipient fibers into silica. Here, we report that the sol–gel transcription of this gel system with tetraethoxysilane (TEOS) results in hollow fiber silica with a 4–5-nm inner diameter, which is comparable to the length of the long axis in **1**. This is a rare example of a unimolecular stack immobilized in an inorganic material.

Sol–gel polycondensation of TEOS was carried out using a gel of **1** and DMF/benzyl alcohol (BnOH) according to the method described previously.^[22] For example, **1** was dissolved in a mixture of DMF, BnOH, and TEOS at 80 °C. This solution gelled when cooled to room temperature. Before the gel was formed, however, benzylamine (BnNH₂) and water were added. In Method A, the mixture was heated at 80 °C again and then left at room temperature for 2 weeks. However, in Method B the mixture was just left at room temperature without the heating treatment. The silica gel thus obtained was washed with methanol to remove organic compounds adsorbed on the outer surface of the silica. After this treatment, the sample (obtained by Method A) was subjected to X-ray photoelectron spectroscopy (XPS) analysis to obtain some information on the outer surface of the silica. The peak corresponding to N atoms at 409 eV (which should result from **1** or benzylamine) was very weak, with the relative intensity of 8:92 to the peak corresponding to Si atoms at 112 eV. This result shows that **1** is scarcely adsorbed on the outer surface of the silica.

The absorption spectrum of **1** (2.3×10^{-6} M) in DMF shows the Soret band at 422 nm and the Q bands at 517, 553, 593, and 647 nm (Figure 1A). When **1** (3.3×10^{-3} M) forms a gel in DMF:BnOH:BnNH₂ = 40:120:3, the spectral shape is significantly broadened and the Soret band shifts to shorter wavelength (397 nm), whereas the Q bands shift to longer wavelength (524, 559, 600, and 656 nm). This spectral change supports the porphyrin–porphyrin stacking interaction in the assembly of **1**.^[25] Interestingly, the absorption spectrum after sol–gel polycondensation (Method A) shows that both the Soret band and the Q bands appear at nearly the same wavelengths as those of the organogel phase. This result implies that the stacked porphyrin structure is still retained in the silica gel phase. This view is further supported by the CD spectra (Figure 1B): the CD spectrum obtained after sol–gel polycondensation is very similar to that of the organogel phase.

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) pictures before and after calcination were used to obtain visual insights into the silica structure. The silica before calcination shows a fibrous structure with an approximate 50-nm outer diameter (Fig-

[*] Prof. Dr. S. Shinkai, S.-i. Tamaru, Dr. M. Takeuchi
Department of Chemistry and Biochemistry
Graduate School of Engineering
Kyushu University
Fukuoka 812-8581 (Japan)
Fax: (+81)92-642-3611
E-mail: seijitcm@mbox.nc.kyushu-u.ac.jp
Dr. M. Sano
Chemotransfiguration Project
Japan Science and Technology Corporation (JST)
Aikawa, Kurume, Fukuoka 839-0861 (Japan)

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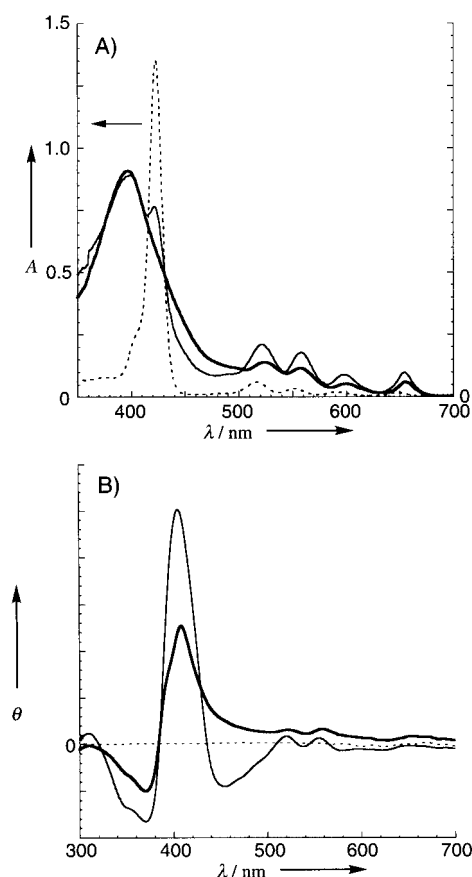


Figure 1. Absorption (A) and CD (B) spectra of silica-coated porphyrin arrays (bold line), organogel of **1** (thin line), and homogeneous solution of **1** (broken line; [**1**] = 2.3×10^{-6} M).

ure 2). This morphology scarcely changed, even after calcination (at 500°C ; see Supporting Information). It is clearly seen from the TEM image (Figure 3) that these silica fibers have an inner hollow with 4–12-nm diameters. Careful examination reveals that there are two different hollow diameters: one about 5 nm, which is comparable with the length of the long axis in **1** (4.2 nm; Figure 3B), and another about 9 nm, which is comparable to twice the length of the long axis, and bearing a stripe in the center (Figure 3C). The TEM image scarcely changed, even after calcination, but the

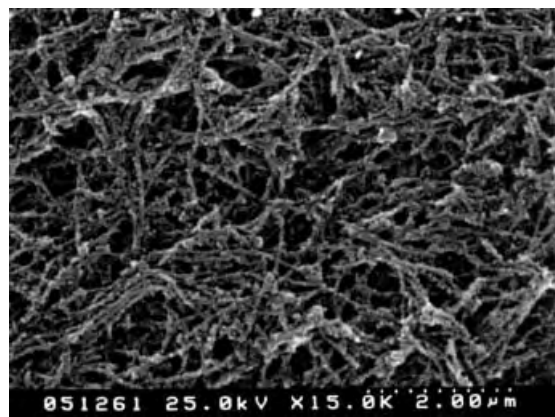


Figure 2. SEM image of silica-coated porphyrin arrays.

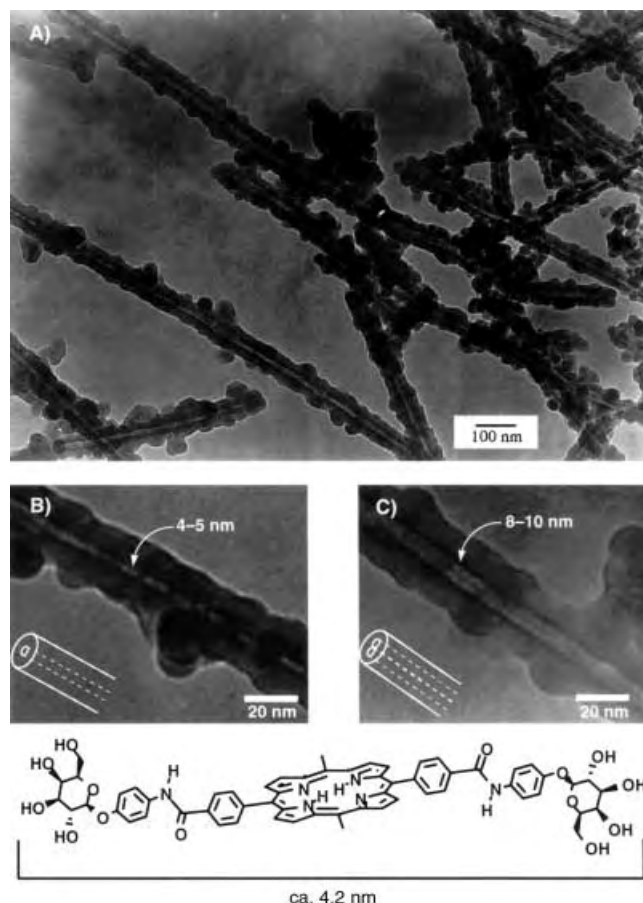


Figure 3. TEM images of silica-coated porphyrin arrays.

central stripe in Figure 3C disappeared (see Supporting Information).

In Method A, the solution containing BnNH_2 (polycondensation catalyst)^[22] was heated so that the formation of bundles of organogel fibers would be suppressed while the rate of sol–gel polycondensation of TEOS would be accelerated. Clearly, this condition facilitates the entrapment of incipient organogel fibers comprised of a unimolecular stack or a bimolecular stack. In the absence of heating after BnNH_2 addition (Method B), the bundle growth of organogel fibers can compete with sol–gel polycondensation to give a helically bundled silica structure from transcription of well-grown, helically bundled organogel fibers (Figure 4).

The results obtained consistently support the view that **1** aggregates into a one-dimensional stack, along which sol–gel polycondensation of TEOS proceeds in the gel phase. The size of the inner hollow obtained in Method A suggests that the incipient organogel fibers are encapsulated in these silica hollow fibers. The disappearance of the central stripe upon calcination is rationalized in terms of the disappearance of stacked **1** molecules by pyrolysis.

In conclusion, we have demonstrated that the elaborate, nanometer-level sol–gel transcription of organic assemblies is possible when the incipient organic assembly can exist stably in the gel phase and when the sol–gel reaction conditions are appropriately selected. Until now, the silica superstructures obtained by template transcription of organic assemblies have



Figure 4. SEM image of the silica structure prepared by transcription of helically bundled **1** as a template (before calcination).

been characterized by the broad size distribution. This polydispersed nature has made their chemical applications difficult. We thus believe that the creation of the new silica fiber structure with the nearly monodispersed hollow size is essential and applicable to other related transcription systems. For example, the nanosized hollow will be useful as a host cavity to enforce molecules to orientate into a one-dimensional direction. This possibility suggests the future possibility of creating various nanosized cavities by designing various sizes of “organic” template molecules.

Experimental Section

Sol–gel polycondensation: Method A: Gelator **1** (4.0 mg) was added to a mixed solvent of DMF (160 μ L) and BnOH (480 μ L) and the mixture was heated until the precipitate was dissolved completely. Tetraethoxysilane (TEOS, 35 μ L), BnNH₂ (10 μ L), and water (10 μ L) were then added to this mixture. The reaction mixture was then reheated until it became homogeneous, and then it was placed at room temperature in the dark for 2 weeks. The product was washed with methanol and dried in vacuo to give the organic–inorganic composite as a purple solid. This sample was calcinated at 150 °C for 2 h, at 500 °C for 5 h under a nitrogen stream, and then at 500 °C for 5 h under an aerobic stream to remove the gelators. The silica thus obtained was colorless.

Method B: Gelator **1** (1.0 mg) was added to a mixture of DMF (40 μ L), BnOH (120 μ L), and TEOS (10 μ L) and the resultant mixture was heated until the precipitate had dissolved completely. The mixture was then cooled to room temperature and BzNH₂ (3 μ L) and water (3 μ L) were added. Without the heating process, this reaction mixture was placed at room temperature in the dark for 2 weeks. The product was washed with methanol and dried in vacuo to give the organic–inorganic composite as a purple solid.

UV/Vis, CD, and X-ray photoelectron spectra were recorded on a Shimadzu UV-2500PC spectrophotometer, a JASCO J-720 spectrometer, and a Perkin–Elmer ESCA 5300 spectrometer, respectively. The SEM and TEM pictures were taken on a Hitachi S-5000 scanning electron microscope and a Hitachi H-600 transmission electron microscope, respectively.

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Intramolecular 1,8-Hydrogen Abstraction Between Glucopyranose Units in a Disaccharide Model Promoted by Alkoxy Radicals**

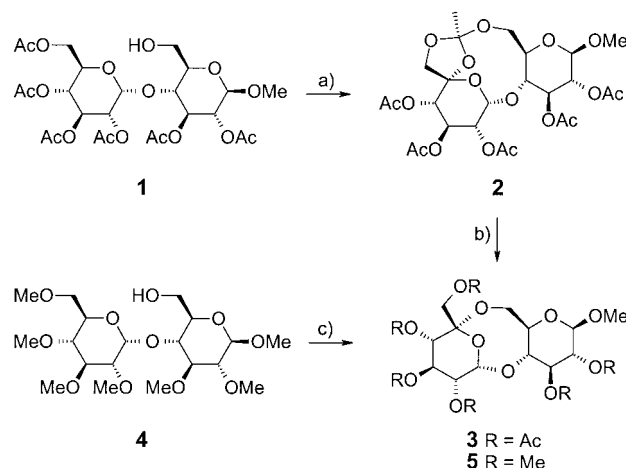
Cosme G. Francisco, Antonio J. Herrera,
Alan R. Kennedy, Daniel Melián, and Ernesto Suárez*

The use of radical reactions in carbohydrate chemistry has recently attracted considerable attention in the synthetic community.^[1] Among free radical reactions intramolecular hydrogen abstraction (IHA) has been comparatively less studied in these systems.^[2] Although 1,*n*-hydrogen transfer has been observed from C_{sp³}-H to alkyl and aryl C radicals for *n* = 4–7,^[3] 1,5-hydrogen transfer is by far the most common IHA reaction when promoted by alkoxy radicals.^[4] In some cases, 1,6-hydrogen transfer from unactivated carbon atoms to alkoxy radicals has been observed, usually in low yield.^[5] Only when the hydrogen atom to be removed is bonded to an oxygen-substituted carbon atom the yield of this last process could be considered to be of synthetic interest.^[6] IHA reactions through eight- or higher membered transition states are practically unknown; entropic effects are probably responsible for the failure of these processes.^[7]

With this in mind, we reasoned that an IHA reaction through an eight- or even higher membered transition state

might be possible in a model with a restricted conformational mobility to avoid the entropic penalty. Two other conditions should be fulfilled: a low-energy transition state and a distance of around 3 Å between the O radical and the hydrogen atom to be abstracted.^[8] It soon became evident that the Glc-α1→4-Glc unit in compound **1** (see Scheme 1)^[9, 10] has a preferred *syn* conformation of the glycosidic bond ($\Phi = -34.2^\circ$, $\Psi = -28.3^\circ$) and a C₆O...HC₅ distance of 2.5 Å in accord with previously reported X-ray crystallographic^[11] and molecular mechanics^[12] analyses of β-D-maltose octaacetate and methyl β-D-maltoside, respectively. A study of the transition state of the C₆O...H-C₅ IHA reaction gave a similar situation for the glycosidic torsion angles ($\Phi = -32.7^\circ$, $\Psi = -37.3^\circ$) and a distance of 3.14 Å between the O radical and H-C₅.^[13]

In order to substantiate our assumption the C₆ alkoxy radical was generated by reaction of the D-maltose derivative **1**^[14] with (diacetoxyiodo)benzene and iodine under irradiation with two 100 W tungsten filament lamps (Scheme 1). The reaction, which proceeds presumably through an alkyl



Scheme 1. IHA under oxidative conditions. a) DIB (1.5 equiv), iodine (0.7 equiv), CH₂Cl₂, *hν*, 25 °C, 90 min, 62%; b) CDCl₃, RT, 60 h, 100%; c) DIB (1.7 equiv), iodine (0.5 equiv), CH₂Cl₂, 25 °C, 90 min, 56%. DIB = (diacetoxyiodo)benzene.

hypoiodite intermediate,^[15] gave orthoacetate **2** in 62% yield. Compound **2** is a moderately stable crystalline solid with an unprecedented 1,3,5,7-tetraoxecane ring system whose structure was elucidated by extensive NMR studies including COSY, TOCSY, DEPT, and HMQC experiments and confirmed by X-ray crystallographic analysis.^[16] The orthoacetate group is hydrolyzed under very mild acidic conditions with concomitant ring contraction to give the 1,3,5-trioxocane derivative **3** in excellent yield. The trioxocane ring adopts a constrained, highly stable boat–chair conformation.^[17] The reaction of the DIB/I₂ system with D-manoside **4**^[18] gave directly the C₅-functionalized disaccharide **5** through a nine-membered transition state (Scheme 1).

The IHA reaction between the two glucopyranose units can also be realized under reductive conditions. In our experience, one of the best methods to generate alkoxy radicals under reductive conditions is by reaction of *N*-hydroxyphthalimide

[*] Prof. E. Suárez, Dr. C. G. Francisco, A. J. Herrera
Instituto de Productos Naturales y Agrobiología del C.S.I.C.
Carretera de La Esperanza 3, 38206 La Laguna, Tenerife (Spain)
Fax: (+34)922-260135
E-mail: esuarez@ipna.csic.es

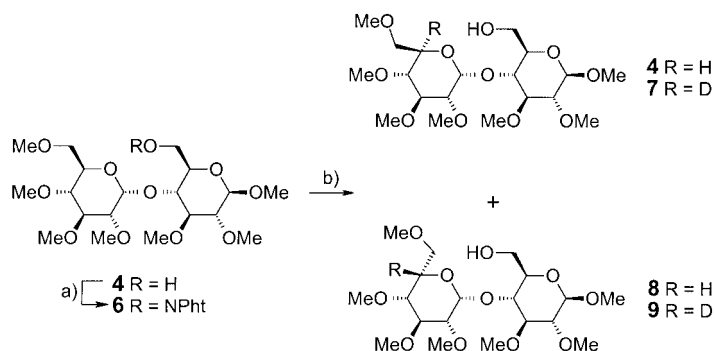
Dr. A. R. Kennedy
Department of Pure and Applied Chemistry
University of Strathclyde
295 Cathedral Street, Glasgow G1 1XL, Scotland (UK)

Dr. D. Melián
Departamento de Química Orgánica
Universidad de La Laguna, Tenerife (Spain)

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derivatives with the $n\text{Bu}_3\text{SnH/AIBN}$ system.^[19] We prepared the phthalimide derivative **6** by treatment of alcohol **4** with *N*-hydroxyphthalimide under Mitsunobu conditions^[20] (Scheme 2). Reduction of compound **6** with $n\text{Bu}_3\text{SnH/AIBN}$ afforded an easily separable mixture of the starting maltose

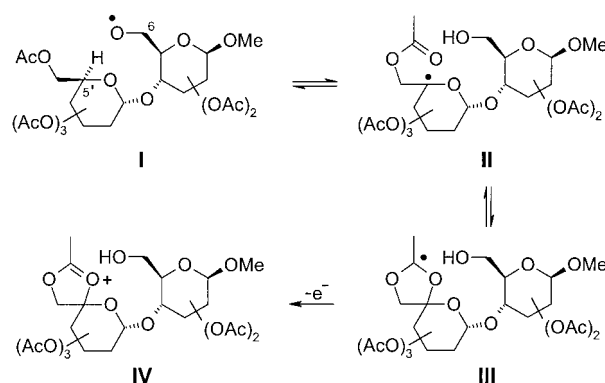


Scheme 2. IHA under reductive conditions. a) DEAD (4 equiv), *N*-hydroxyphthalimide (4 equiv), PPh_3 (4 equiv), THF, 0 °C, 30 min, 82 %; b) $n\text{Bu}_3\text{SnH}$ or $n\text{Bu}_3\text{SnD}$ (9 equiv), AIBN (0.16 equiv), C_6H_6 , reflux, 1 h, 86–78 %. DEAD = diethyl azodicarboxylate, AIBN = azobisisobutyronitril.

derivative **4** and a new disaccharide **8** with inversion of configuration at C_5 . It is worth noting that by using this simple protocol the second D-glucosyl moiety in the maltose derivative **4** has been transformed into a rare β -L-idosyl monosaccharide unit. As can be easily observed by NMR spectroscopy, epimerization of the C_5 side chain triggers inversion of the pyranose ring chair conformation. The conformation changes from ${}^4\text{C}_1$ in the α -D-glucosyl unit to ${}^1\text{C}_4$ in the β -L-idosyl moiety, which leaves the C_2 , C_3 , and C_4 substituents in axial positions.^[21]

To unambiguously verify the structure of **8** and clarify the reaction mechanism, we used $n\text{Bu}_3\text{SnD}$ as reductant and obtained compound **9** with exclusive and quantitative incorporation of deuterium at the C_5 position. In addition, the maltose derivatives **7** and **4** were obtained in a ratio of 57:43, compound **4** being formed by reduction of the alkoxy radical before the IHA reaction could take place. The deuterium position was determined NMR spectroscopically not only by the D- C_5 coupling but also by the small yet significant displacement of the signals of the adjacent C_4 and C_6 carbon atoms in the ${}^{13}\text{C}$ NMR spectra.^[22] These results have also allowed us to estimate a 60 % yield for the hydrogen abstraction reaction.

The mechanism depicted in Scheme 3 has been proposed for the formation of the orthoacetate derivative **2**. Initially the C_6 alkoxy radical **I** abstracts specifically the hydrogen atom at C_5 to give an alkyl radical **II** which adds intramolecularly to the carbonyl oxygen giving the 1,3-dioxan-2-yl radical **III**. This radical is oxidized with an excess of reagent to the oxycarbenium ion **IV**, which is subsequently trapped by the primary hydroxy group at C_6 to give the orthoacetate **2**. This intuitive stepwise ring closure through a dioxanyl radical has been excluded from a related β -(acyloxy)alkyl rearrangement in favor of an ion pair mechanism.^[23] In our case, a tight ion pair intermediate which eventually could collapse to the



Scheme 3. Proposed mechanism for the IHA according to Scheme 1.

oxycarbenium **IV** under the oxidative reaction conditions used cannot be ruled out. In the case of hepta-*O*-methylmaltose derivative **4** the C_5 radical initially formed is rapidly oxidized to a carbenium ion, which is stabilized as an oxycarbenium ion by the adjacent oxygen atom of the pyranose ring. This ion adds, exclusively through its *si* face, to the primary hydroxy group to afford the 1,3,5-trioxocane **5**.

In this paper we have demonstrated the possibility to modify specifically one sugar unit in a D-Glc- α 1 $\rightarrow$ 4-D-Glc disaccharide. The disaccharide L-ido- β 1 $\rightarrow$ 4-D-Glc (**8**) obtained may be of interest in the chemistry of heparin analogs since the L-iduronic- β 1 $\rightarrow$ 4-D-Glc unit is present as a repetitive fragment in this polysaccharide.^[24] We believe that the very mild IHA reaction presented here can be extended to other α 1 $\rightarrow$ 4 disaccharides and presumably to other systems that fulfill the aforementioned conditions. Although the yields are moderate the obtained compounds are difficult to prepare by other methods; there synthesis requires in general relatively complex processes. Of particular interest is that the reactions can be realized under oxidative and under reductive conditions since this gives some synthetic control over the fate of the C_5 radical.

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A New Catalyst for the Selective Oxidation of Butane and Propane**

Mark E. Davis,* Christopher J. Dillon,
Joseph H. Holles, and Jay Labinger

The abundance and low cost of light alkanes has motivated the search for new catalytic materials that can accomplish selective oxidation processes. The conversion of *n*-butane to maleic anhydride over V-P-O catalysts with molecular oxygen is commercially well established.^[1] Other reactions of current interest are the production of acetic acid from ethane and acrylic acid from propane. Polyoxometalates are among the numerous catalytic materials that have been extensively investigated for each of the aforementioned reactions. Typically different polyoxometalate compositions have been used for each alkane. These compounds (and other mixed-metal oxides) have not been found to perform as well as V-P-O catalysts for the conversion of *n*-butane to maleic anhydride,^[2] or as well as mixed-metal oxides containing Mo-V-Nb-Te^[3a,b] or Mo-V-Nb-Sb^[4] for conversion of propane to acrylic acid.

We have discovered a new catalyst system that achieves selective oxidation of both *n*-butane and propane. Li et al. reported that a solid obtained by treating molybdophosphoric acid, H₃PMo₁₂O₄₀ (henceforth denoted as PMo₁₂) with pyridine followed by activation in nitrogen at 420 °C exhibits catalytic activity for oxidation of propane to acrylic acid.^[5] Ueda and Suzuki also showed that molybdovanadophosphoric acid (denoted as PMo₁₁V) similarly treated gives a less active and selective catalyst.^[6] Our catalysts are obtained from PMo₁₂ and PMo₁₁V (prepared by known methods^[7]), exchanged sequentially with niobium oxalate (giving NbPMo₁₂ and NbPMo₁₁V) and pyridine (giving NbPMo₁₂pyr and NbPMo₁₁Vpyr) in aqueous media, followed by heating to 420 °C in flowing helium. The elemental compositions of the solids thus obtained are typically Nb_{0.1–0.25}PMo₁₂(pyr)_{3–4} or Nb_{0.1–0.25}PMo₁₁V(pyr)_{3–4} within experimental error.

Table 1 reports the catalytic performance of various materials for *n*-butane oxidation under hydrocarbon-rich conditions (C₄/O₂ = 2/1). All the solids prepared from precursors containing both pyridine and niobium are very active and selective. Note particularly the high space time yield (STY) for NbPMo₁₂pyr and NbPMo₁₁Vpyr achieved by increasing the total flow rate by a factor of eight (15 mL min^{−1} to 120 mL min^{−1}; see entries 6 and 7, and 13 and 14, respectively, in Table 1). In contrast, the polyoxometalates that have not been exposed to pyridine do not exhibit significant activity (entries 1, 2, 8, and 9, Table 1), while samples treated with pyridine but without niobium do not give the highest activities

[*] Prof. M. E. Davis, C. J. Dillon, J. H. Holles

Chemical Engineering
California Institute of Technology
Pasadena, CA 91125 (USA)
Fax: (+1) 626-568-8743
E-mail: mdavis@cheme.caltech.edu

Dr. J. Labinger
Beckman Institute
California Institute of Technology
Pasadena, CA 91125 (USA)

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Table 1. Reactivity of *n*-butane.

Entry	Catalyst	<i>T</i> [°C]	Flow rate [mL min ⁻¹] ^[a]	Conversion [%]		CO _x	Ac	Selectivity [%] ^[c]		STY ^[d]
				C ₄	O ₂			AA	MA	
1	PMo ₁₂	380	4:2:4:5	0.2	7	64	34	2	—	—
2	NbPMo ₁₂	380	4:2:4:5	3	32	13	7	2	70	0.017
3	PMo ₁₂ pyr	380	4:2:4:5	13.5	89	14	3	1	82	0.097
4	PMo ₁₂ pyr	340	4:2:4:5	7	55	10	4	1	83	0.050
5	NbPMo ₁₂ pyr	380	4:2:4:5	15 ^[b]	100	25	3	1	71	0.084
6	NbPMo ₁₂ pyr	380	32:16:32:40	15 ^[b]	100	5	3	1	90	0.840
7	NbPMo ₁₂ pyr	340	32:16:32:40	14	91	6	4	1	89	0.840
8	PMo ₁₁ V	380	4:2:4:5	0.5	9	31	17	—	50	1.6 × 10 ⁻³
9	NbPMo ₁₁ V	380	4:2:4:5	0.4	9	42	19	4	25	6.3 × 10 ⁻⁴
10	PMo ₁₁ Vpyr	380	4:2:4:5	13.5	90	5	3	1	90	0.11
11	PMo ₁₁ Vpyr	340	4:2:4:5	2	29	16	4	1	78	0.013
12	NbPMo ₁₁ Vpyr	380	4:2:4:5	15 ^[b]	100	16	5	2	76	0.090
13	NbPMo ₁₁ Vpyr	380	32:16:32:40	14	95	9	5	3	80	0.760
14	NbPMo ₁₁ Vpyr	340	32:16:32:40	13	83	26	10	4	59	0.560

[a] *n*-Butane:oxygen:helium:water. [b] Theoretical maximum conversion. [c] Abbreviations: C₄: *n*-butane; CO_x: carbon oxides; Ac: acetic acid; AA: acrylic acid; MA: maleic acid. [d] Space time yield of maleic acid [mmol min⁻¹ g⁻¹ of catalyst].

(entries 3, 4, 10 and 11, Table 1). Although the niobium content may vary, Nb/P ratios nearer to 0.25 gave higher activities. The presence of vanadium appears to have little influence on the reactivity of *n*-butane.

Table 2 compares the reactivity of *n*-butane over the new catalysts reported here to several of those given in the literature. The new catalysts exhibit substantially higher productivities (STY, entries 3 and 4, Table 2) and at least comparable selectivities, as well as the ability to operate at lower temperatures (300 °C; entry 5, Table 2). In addition to the hydrocarbon-rich conditions reported in Table 1, the new catalysts perform well in more typically studied hydrocarbon-lean environments (C₄/O₂ = 1/10; entry 6, Table 2).

Unlike most previous examples, these new catalysts are effective for more than one reactant: propane is also selectively oxidized to a variety of partially oxidized products

(see Table 3). As with *n*-butane, the catalyst precursor that contains both niobium and pyridine gives the most active catalyst (entry 4, Table 3). Interestingly, in addition to forming acrylic and acetic acids, the new catalyst produces substantial amounts of maleic acid. Results using propene, 1,5-hexadiene, and ¹³C-labeled propane in individual experiments as feed hydrocarbons suggest that maleic acid is formed by the reaction sequence shown in Scheme 1.

Table 4 compares the reactivity results from the new catalyst to some of the more selective propane oxidation catalysts that have been reported. Since the literature data are at different reaction conditions, for example, propane/O₂, propane concentration, temperature, residence time, etc., it is difficult to compare, but it is clear that while the catalyst reported here is not the most selective, it has exceptional productivity for acrylic acid (AA STY).

Table 2. Reactivity of *n*-butane over various catalysts.

Entry	Catalyst	<i>T</i> [°C]	Flow rate [mL min ⁻¹] ^[a]	Conversion [%]		CO _x	Ac	Selectivity [%]		STY ^[c]
				C ₄	O ₂			AA	MA	
1	MoO ₃	380	4:2:4:5	0.7	20	95	2.4	—	—	—
2	PMo ₁₂	380	4:2:4:5	0.2	7	64	34	2	—	—
3	NbPMo ₁₂ pyr	380	32:16:32:40	15 ^[b]	100	5	3	1	90	0.840
4	NbPMo ₁₁ Vpyr	380	32:16:32:40	14	95	9	5	3	80	0.760
5	NbPMo ₁₁ Vpyr	300	4:2:4:5	9	75	26	12	2	60	0.033
6	NbPMo ₁₁ Vpyr	340	1:10:35:5	62	61	50	3.8	0.8	46	0.019
7	VPO ^[8]	380	4:6:26:0	30	—	8	—	—	80	0.067
8	BiPMo ₁₂ O ₄₀ + 2VO ²⁺ ^[9]	360	6.3:58:218:34	31.8	—	37	17	14	32	0.001
9	H ₃ PMo ₁₀ V ₂ O ₄₀ ^[10]	340	0.6:5.4:24:0	90	—	—	—	—	38	0.003

[a] *n*-Butane:oxygen:helium:water. [b] Theoretical maximum conversion. [c] Space time yield of maleic acid [mmol min⁻¹ g⁻¹ of catalyst].

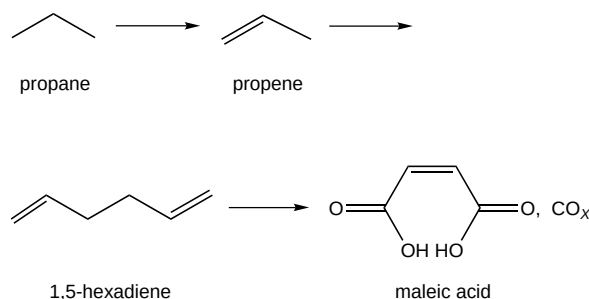
Table 3. Reactivity of propane at 380 °C.^[a]

Entry	Catalyst	Conversion [%]		CO _x	Selectivity [%] ^[d]					Yield [%] AA	STY ^[e] AA
		C ₃	O ₂		C ₂	C ₃	Ac	AA	MA		
1	PMo ₁₁ V ^[b]	0.4	3.4	30	12	54	4	—	—	—	—
2	NbPMo ₁₁ V ^[b]	1.4	5.7	22	6	44	16	10	—	0.1	1.39 × 10 ⁻³
3	PMo ₁₁ Vpyr ^[b]	3.4	10.1	10	4	37	30	17	—	0.6	5.55 × 10 ⁻³
4	NbPMo ₁₁ Vpyr ^[c]	20.9	68.7	8	—	—	24	50	16	10.5	0.623

[a] C₃/O₂/He/H₂O = 4:2:4:5 (mol %). [b] Total flow rate = 15 mL min⁻¹; residence time = 0.42 s; total gas hourly space velocity (GHSV) = 9000 h⁻¹. [c] Total flow rate = 120 mL min⁻¹; residence time = 0.10 s; total GHSV = 36000 h⁻¹. [d] Abbreviations: C₃: propane; CO_x: carbon oxides; C₂: ethene; C₃: propene; Ac: acetic acid; AA: acrylic acid; MA: maleic acid. [e] STY = mmol acrylic acid min⁻¹ g⁻¹ of catalyst.

Table 4. Reactivity of propane over various catalysts.

Entry	Catalyst	C ₃ :O ₂ :inert:H ₂ O [mL min ⁻¹]	Residence time [s]	C ₃ Conv. [%]	AA sel. [%]	AA yield [%]	AA STY [mmol min ⁻¹ g ⁻¹]	Ref.
1	PMo ₁₂	10:5:25:10	3.6	8	29	2	2.70 × 10 ⁻³	6
2	MoSbVNbO _x	2.0:3.2:11.8:28.0	2.0	31	30	9	4.86 × 10 ⁻³	4
3	MoVNbTeO _x	0.6:2.0:7.4:8.8	1.9	80	61	49	0.018	3b
4	CsFe(PMo ₁₁ VO ₄₀)	4.5:7.5:3.0:0	4.0	47	28	13	0.024	11
5	NbPMo ₁₁ Vpyr	32:16:32:40	0.1	21	50	11	0.623	this work



Scheme 1. Proposed sequence for the conversion of propane to maleic acid by the new catalysts.

At this time the nature of the active sites in these highly active catalysts is unknown. All the pyridine is removed by heating in helium to 420 °C. The pyridine acts as a reductant to lower the average oxidation states of vanadium (if present), molybdenum, and niobium (ascertained by using EPR, NMR, UV/Vis, and XANES studies). Heating under oxidizing conditions up to 420 °C renders the solids catalytically inactive; thus, reducing pretreatment conditions are necessary. Other amines can be used as reductants, but pyridine is the best found thus far. Exposure to temperatures above approximately 420 °C even in inert environments causes phase transitions ultimately leading to crystalline molybdenum oxides (from X-ray powder diffraction) that are not active catalysts.

The excellent performance in terms of yield and (especially) productivity, the versatility with respect to alkane feedstock, and the synthesis from precursors that are not only of well-defined composition and structure but also are amenable to a number of potentially informative spectroscopic and other methods for characterization, all strongly indicate that these new materials offer great promise towards the important goal of developing improved catalysts for selective oxidation. Further work towards extending the scope of catalytic reactivity, optimizing performance, and understanding the mechanism is ongoing.

Experimental Section

Preparation of NbPMo₁₁Vpyr: Sodium hydrogen phosphate (7.098 g, 50 mmol) was dissolved in water (100 mL) at room temperature and sodium metavanadate (6.097 g, 50 mmol) was dissolved in water (100 mL) at 80 °C. The two solutions were combined at room temperature and the mixture was acidified with concentrated sulfuric acid (5 mL), which led to a dark red solution. Sodium molybdate dihydrate (133.1 g, 550 mmol) was dissolved in water (200 mL) at room temperature and the solutions were combined. Concentrated sulfuric acid (85 mL) was added to the solution over 90 min (exotherm) with vigorous stirring. This generated a clear bright red solution that was added to diethyl ether (200 mL) in a separating funnel

and shaken. This resulted in three phases, from which the dark red layer was decanted and retained. The aqueous layer was extracted twice, and the ethereal fractions were combined. The diethyl ether was removed resulting in a thick red syrup that was dissolved in water and recrystallized. The orange crystals of PMo₁₁V were dried at 100 °C overnight. Niobium pentachloride (1.210 g, 4.48 mmol) was dissolved in water (10 mL) and the solution basified by using ammonium hydroxide (0.5 mL). The white precipitate was removed by filtration and dissolved in oxalic acid (1.008 g, 11.2 mmol in 20 mL water). The niobium oxalate solution was then slowly added to 11-molybdo-1-vandaniophosphoric acid (PMo₁₁V; 20 g) dissolved in water (40 mL). The mixture was stirred and heated to 80 °C until the liquid had evaporated. An aqueous solution of pyridine (1.645 g, 20.8 mmol in 10 mL water) was slowly added to a slurry of the niobium polyoxometalate NbPMo₁₁V (5.260 g) in water (30 mL) to form an immediate precipitate. The mixture was stirred and evaporated to dryness at 80 °C.

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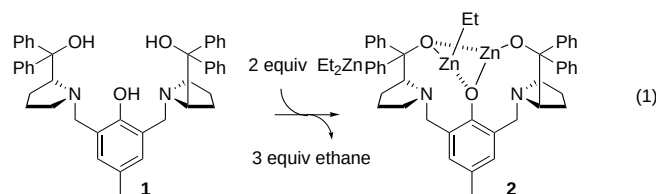
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A Dinuclear Zn Catalyst for the Asymmetric Nitroaldol (Henry) Reaction**

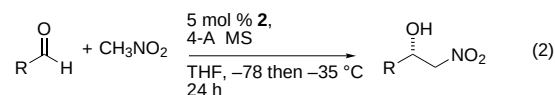
Barry M. Trost* and Vince S. C. Yeh

The nitroaldol (Henry) reaction is a fundamental synthetic tool for the construction of C–C bonds.^[1] The diversity of the transformations of the adducts, such as reduction to amines or Nef reaction to carbonyl compounds, provides numerous applications of this process. Like the aldol reaction, it may be highly atom economic.^[2] In spite of the many applications, the catalytic enantioselective variant of the nitroaldol reaction is relatively under-developed compared to its aldol reaction counterpart. Shibasaki and co-workers have reported a series of heterobimetallic catalysts that proved to be effective for asymmetric Henry reactions.^[3] We have recently reported the development of a novel type of asymmetric catalyst (**2**, see Equation (1)) which involves a dinuclear zinc complex center with a chiral semi-azacrown ligand. This catalyst has been successfully applied in enantioselective, direct aldol reactions involving various ketone nucleophiles and aldehyde electrophiles.^[4] To the best of our knowledge, zinc catalysts and/or mediators have not been employed for the Henry reaction. Herein we explore the applicability of **2** in catalytic enantioselective Henry reactions.

The catalyst is prepared by treating phenol **1** with two equivalents of diethylzinc wherein three equivalents of ethane [Eq. (1)] evolve. The solution of this complex is then added



directly into the reaction solution containing nitromethane and the aldehyde substrate. The nitroaldol reaction between nitromethane and cyclohexylcarboxaldehyde [Eq. (2), R = cyclohexyl] was explored to determine the optimal conditions. Table 1 summarizes the results of the initial studies. The data clearly demonstrates the superiority of THF as solvent in



[*] Prof. B. M. Trost, V. S. C. Yeh
Department of Chemistry
Stanford University
Stanford, CA 94305-5080
Fax: (+1) 650-725-0259
E-mail: bmtrost@stanford.edu

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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. Optimization of the nitroaldol reaction between nitromethane and cyclohexanecarboxaldehyde.^[a]

Entry	CH ₃ NO ₂ [Equiv]	Catalyst [mol %]	T [°C]	Solvent	Yield [%]/ ee [%] ^[b]
1	10	5	5	THF	69/78
2	10	5	–20	THF	68/85
3	10	5	–20	toluene	68/57
4	10	5	–20	CH ₂ Cl ₂	75/51
5	2	5	–20	Et ₂ O	20/55
6	2	5	–20	THF:dioxane 4:1	17/86
7	10	5	–78 then –20	THF	75/85
8	10	2.5	–78 then –20	THF	44/85
9	6	5	–78 then –20	THF	70/86

[a] All reactions were run on 1 mmol scale at 0.33 m in aldehyde in the presence of 100 mg of 4-Å MS. [b] Enantiomeric excess determined by chiral HPLC using chiralcel OD column.

terms of yield and *ee* values (entries 1 and 2) compared to other solvents (entries 3–6). The minimum amount of nitromethane and catalyst that could be used to obtain a reasonable yield of the product within a 24 h time frame were five equivalents and 5 mol %, respectively. In the cases where yields were low (entries 5, 6, and 8), the aldehyde was recovered unchanged. Temperature played a significant effect on the *ee* value of the product. Lowering the temperature of the reaction from 5 to –20 °C (entry 1 versus 2) significantly increased the *ee* value. Furthermore, pre-cooling the reaction to –78 °C during the addition of the catalyst insures consistent *ee* values for each individual run.^[5] The addition of 4-Å molecular sieves (100 mg per 1 mmol of aldehyde) was employed in all reactions. The use of additives^[4] such as Ph₃PS or CF₃CH₂OH proved not to be beneficial in terms of either yield or *ee* value.

Table 2 and Equation (2) summarize the results for a number of examples. α -Branched aldehydes gave nitroaldol products in high yields and high *ee* values (entries 3 and 4). Aldehydes with no α branch were generally more challenging substrates. However, reasonable yields were obtained by using 15 equivalents of nitromethane instead of 10, and by using more concentrated solutions in the reaction (entries 6 and 7). The *ee* value of product **8** (entry 6) could be increased to 96% by one recrystallization. The product **9** (entry 7) is a useful bifunctional molecule that could serve as a starting material for the rapid access to an unusual GABOB amino acid.^[6] Aromatic and heterocyclic aldehydes also gave nitroaldol products in good yields and good *ee* value as well (entries 8–11). The product **12** (entry 10) may be used as the starting material for the synthesis of arbutamine.^[7] The use of (*R*)-**14** and (*S*)-**15** (citronellal) [Eqs. (3) and (4)] deals with the

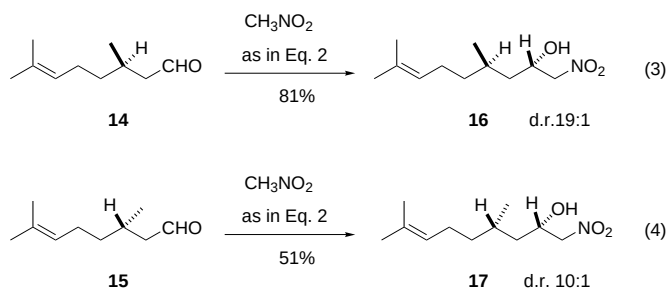


Table 2. Enantioselective nitroaldol reaction with CH_3NO_2 .^[a]

Entry	R	Product	Yield [%] ^[c]	ee [%] ^[b]
1			75	85
2 ^[c]			58	88
3 ^[c]			88	93
4			90	92
5			84	87
6 ^[d]			56	85
6 ^[e]			59	84
7 ^[d]			56	86
8			75	91
9			71	93
10			69	78
11			79	90

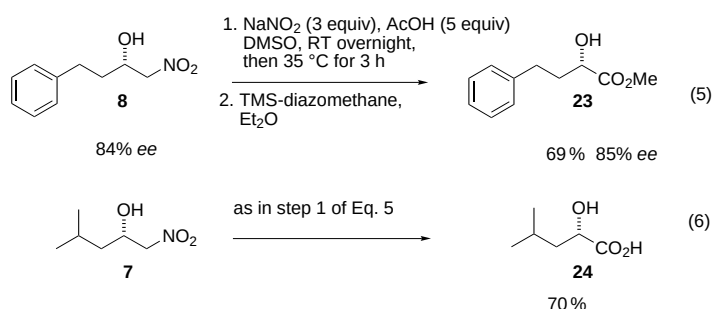
[a] All reactions were carried out on a 1-mmol scale using 5 mol % catalyst, 10 equiv CH_3NO_2 in 0.33 M THF solution at -35°C for 24 h unless noted otherwise. [b] Determined by chiral HPLC. See Supporting information for details. [c] Reaction performed using 5 equiv CH_3NO_2 at -60°C . [d] Reaction performed using 15 equiv CH_3NO_2 and 5 mol % catalyst in 0.66 M THF solution at -35°C for 2 days. [e] Same as [a], except using 10 mol % catalyst in 0.33 M THF solution. [f] The product had 96% ee after one recrystallization from Et_2O :hexane.

issue of controlling the diastereoselectivity. The catalyst indeed controls the facial selectivity. Interestingly, the selectivity in forming the *anti* diastereomer **16** is higher than forming the *syn* diastereomer **17**, but in both cases, the major epimer of the alcohol has the *S* configuration. This difference is understandable on the basis of the enhanced steric strain associated with the *syn* isomer compared to the *anti* isomer.

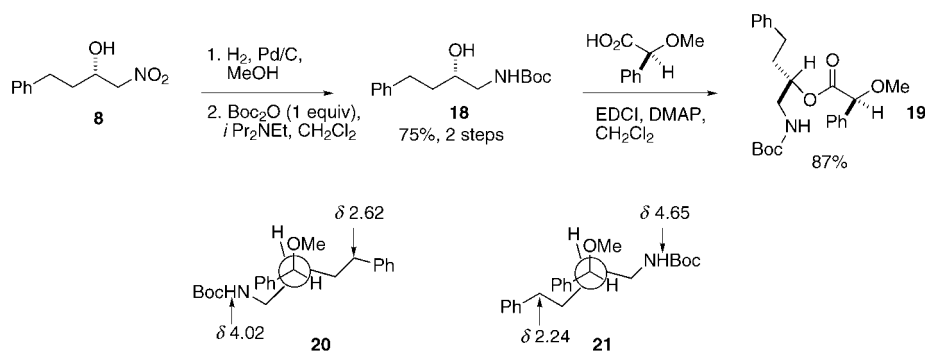
The absolute configuration of the nitroaldol adducts **3** was assigned by comparison to literature compounds.^[3a] Additional analysis were made on the nitro alcohols **4**, **8**, and **16** by the *O*-methyl mandelate

method.^[8] For example, enantiomerically enriched **8** was converted into the corresponding (*S*)-*O*-methyl mandelate **19** as shown in Scheme 1.^[9] Racemic **8** was converted into a diastereomeric mixture of mandelates, shown in extended Newman projections **20** and **21**. The absolute configuration of the newly generated stereogenic center of the nitroaldol products using the (*S,S*)-ligand **1** could be assigned from ^1H NMR correlation results as “*S*” (as depicted). It is likely that the absolute configuration of the remaining examples are the same.

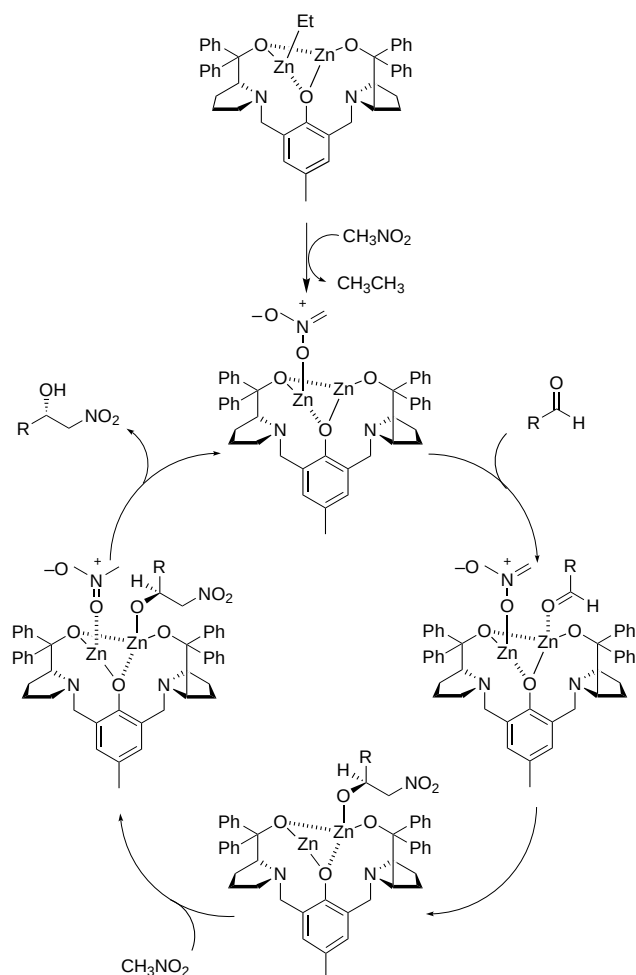
The nitroaldol products could also be further elaborated into chiral α -hydroxy acids by sodium nitrite in acetic acid and dimethyl sulfoxide (DMSO)^[10] without epimerization of the stereogenic center [Eqs. (5) and (6); TMS = trimethylsilyl].



The dinuclear zinc complexes of ligand **1** (namely, **2**) are indeed effective for the addition of nitromethane to aldehydes. The facial selectivity is the same as that observed in the aldol reaction. The lack of structural information on the catalytic active species makes the development of a model to understand this selectivity difficult. Nevertheless, a catalytic cycle as depicted in Scheme 2 may be envisioned, and accounts for the observations. This new catalyst system provides a ready entry to this important building block, which has been used for the asymmetric synthesis of β -hydroxyamines as well as α -hydroxycarboxylic acids. While further work to define the source of the asymmetric induction and scope of the reaction with substituted systems is planned, the current version involving nitromethane has already proven to be useful, and has been shown to be effective for the broadest array of aldehydes examined to date.



Scheme 1. Determination of the absolute configuration of nitro alcohol **8**. Boc = *tert*-butoxycarbonyl, EDCI = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, DMAP = 4-dimethylaminopyridine.



Scheme 2. Proposed catalytic cycle.

Experimental Section

Typical experimental procedure: A solution of diethylzinc (0.36 mL, 1.1 M in toluene, 0.4 mmol) was added to a stirred and cooled (0 °C) solution of **1** (0.128 g, 0.2 mmol) in THF (2 mL) under an argon atmosphere. After the addition, the cold bath was removed and the solution was stirred at room temperature for 30 min to form a solution of **2** (ca. 0.1 M).

A solution of the zinc catalyst **2** (0.5 mL, 0.1 M in THF, 0.05 mmol) was added dropwise to a stirred and cooled (−78 °C) suspension of powdered

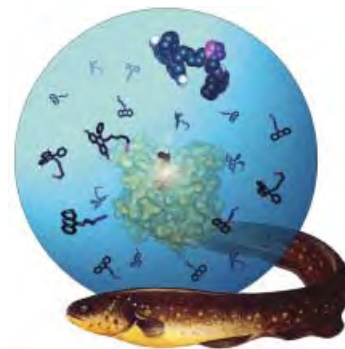
molecular sieves (4 Å; 100 mg, dried at 120 °C under vacuum overnight), cyclohexanecarboxaldehyde (0.112 g, 1 mmol), and CH₃NO₂ (0.32 mL, 6 mmol) in THF (3 mL) under an argon atmosphere. After the addition, the resulting mixture was transferred to a −20 °C cold bath and left stirring for 24 h. The reaction was quenched by adding aqueous HCl solution (3 mL, 0.5 M), and the resulting mixture was partitioned with Et₂O (10 mL). The organic phase was washed with water and brine, then dried (MgSO₄) and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc:petroleum ether, 1:9) to afford the nitroaldol product **3**^[a] (0.12 g, 70%) as a clear oil: [α]_D²⁵ = +15.87 (c = 5.01, CHCl₃) (86% ee); ¹H NMR (300 MHz, CDCl₃): δ = 1.0–1.34 (m, 5 H), 1.40–1.54 (m, 1 H), 1.61–1.85 (m, 5 H), 2.58 (brs, 1 H), 4.02–4.12 (m, 1 H), 4.35–4.50 (m, 2 H); ¹³C NMR (75.5 MHz, CDCl₃): δ = 25.69, 25.82, 26.02, 27.89, 28.75, 41.37, 42.81, 79.28; t_r = 16.81 and 17.64 min (major; Chiralcel OD, λ = 254 nm, heptane:isopropanol 97:3, 1 mL min^{−1}).

Received: November 12, 2001 [Z18201]

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- [11] We thank Nadine Bremeyer for preparing compound **13**.

COVER PICTURE

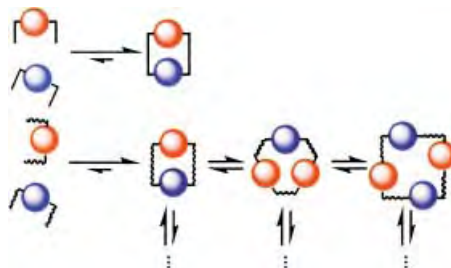
The cover picture shows the electric eel, *Electrophorus electricus*, a source for commercially available acetylcholinesterase. In an experiment described by K. B. Sharpless and M. G. Finn and co-workers on pp. 1053–1057, a femtomolar inhibitor was assembled by the enzyme from a collection of building blocks containing azide and alkyne functional groups, shown floating in solution. The templated 1,3-dipolar cycloaddition reaction, producing the inhibitor, is represented by the flare of light at the center of the image.



REVIEW

Contents

Supramolecular chemistry at the covalent level! That is the mouth-watering prospect that dynamic covalent chemistry offers the chemist. Covalent synthesis under thermodynamic control can either result in the self-assembly of a single molecular architecture (see scheme, top), if the monomer is rigid and correctly predisposed, or the formation of adaptable libraries (bottom), if the monomer contains some flexibility programmed into it.



Angew. Chem. 2002, 114, 938–993

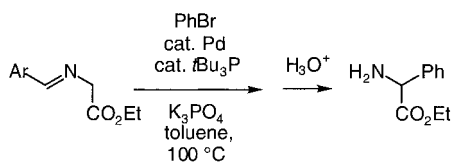
S. J. Rowan,* S. J. Cantrill,
G. R. L. Cousins, J. K. M. Sanders,
J. F. Stoddart 898–952

Dynamic Covalent Chemistry

Keywords: catenanes • combinatorial libraries • macrocycles • polymers • rotaxanes • supramolecular chemistry

HIGHLIGHTS

Fine tuning for fine chemicals: Two complimentary and yet intimately related methods for the palladium-catalyzed arylation of esters and their derivatives have emerged. The careful choice of ligand and base proved to be decisive; the scheme shows one variation of one of the methods, which leads to amino esters. These results confirm, yet again, that the repertoire of palladium catalysis continues to expand at an astonishing pace.



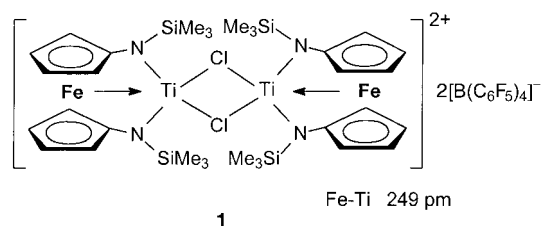
Angew. Chem. 2002, 114, 995–998

G. C. Lloyd-Jones* 953–956

Palladium-Catalyzed α -Arylation of Esters: Ideal New Methodology for Discovery Chemistry

Keywords: amino acids • arylation • esters • homogeneous catalysis • palladium • synthetic methods

The search for catalysts for olefin polymerization has brought complexes into the limelight that contain anionic 1,1'-ferrocenedi(amido) chelate ligands. The stabilization of cationic titanium centers by such a chelate ligand may lead to the formation of a dative Fe $\rightarrow$ Ti heterodimetallic bond, as in the cation of the salt **1**.



1

Fe-Ti 249 pm

Angew. Chem. 2002, 114, 998–1000

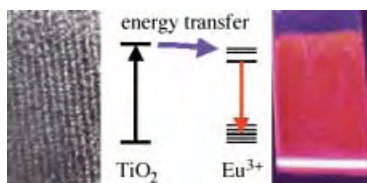
M. Herberhold* 956–958

1,1'-Ferrocenedi(amido) Chelate Ligands in Titanium and Zirconium Complexes

Keywords: amido ligands • chelates • ferrocenes • metal–metal interactions • sandwich complexes

The well-ordered array of pores and walls

made up of nanocrystallites in a mesoporous titania thin film can be doped with high concentrations of Eu^{3+} (up to 8 mol %) to create a bright red photoluminescent material (see picture). The photoluminescence arises from energy transfer through excitation of the titania nanocrystallites in their band gap to the crystal field states of the europium ions; photoluminescence concentration quenching is prevented because of the high surface area and nanocrystalline structure of the material.



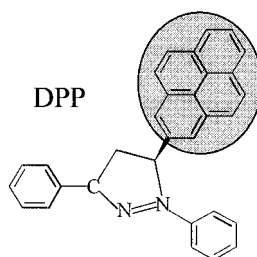
K. L. Frindell, M. H. Bartl, A. Popitsch, G. D. Stucky* 959–962

Sensitized Luminescence of Trivalent Europium by Three-Dimensionally Arranged Anatase Nanocrystals in Mesostructured Titania Thin Films

Keywords: europium • luminescence • mesoporous materials • nanocrystallites • titanium

Angew. Chem. **2002**, *114*, 1001–1004

Tunable, multiple emission is exhibited by nanoparticles of 1,3-diphenyl-5-pyrenyl-2-pyrazoline (DPP; see picture), which ranges from near-UV to green. Tuning could be effected by alteration of either the excitation wavelength or the nanoparticle size. In contrast, DPP in dilute solution only showed the emission characteristics of the pyrene chromophore. In bulk crystals, only the emission characteristics of the pyrazoline chromophore were exhibited.



H. Fu, B. H. Loo, D. Xiao, R. Xie, X. Ji, J. Yao,* B. Zhang, L. Zhang ... 962–965

Multiple Emissions from 1,3-Diphenyl-5-pyrenyl-2-pyrazoline Nanoparticles: Evolution from Molecular to Nanoscale to Bulk Materials

Keywords: charge transfer • fluorescence • nanostructures • photochemistry

Angew. Chem. **2002**, *114*, 1004–1007

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>

Surface Structure and Crystal Growth in Zeolite Beta C

B. Slater,* R. A. Catlow, Z. Liu, ♦
T. Ohsuna, O. Terasaki,
M. A. Camblor

Semiconductor Nanohelices Templated by Supramolecular Ribbons

E. D. Sone, E. R. Zubarev,
S. I. Stupp*

Phase-Sensitive Supramolecular Chirogenesis in Bisporphyrin Systems

V. V. Borovkov,* T. Harada,
Y. Inoue, R. Kuroda*

The Stable Pentamethylcyclopentadienyl Cation

J. B. Lambert,* L. Lin,
V. Rassolov

Polymeric Surfactants for the New Millennium: A pH-Responsive, Zwitterionic, Schizophrenic Diblock Copolymer

S. Liu, S. P. Armes*

Cyclo[8]pyrrole: A Simple-to-Make Expanded Porphyrin with No *meso* Bridges

D. Seidel, V. Lynch, J. L. Sessler*

Cyclotetrasilene Ion: A Reversible Redox System of Cyclotetrasilene Cation, Radical, and Anion

T. Matsuno, M. Ichinohe,
A. Sekiguchi*

Previously unrecognized chiral and rotational twinning were revealed by optical microscopy, synchrotron white beam X-ray topography, and crystallography in the crystal structure of the inclusion compound of 2,12-tridecanedione/urea (see picture), which was otherwise intractable.



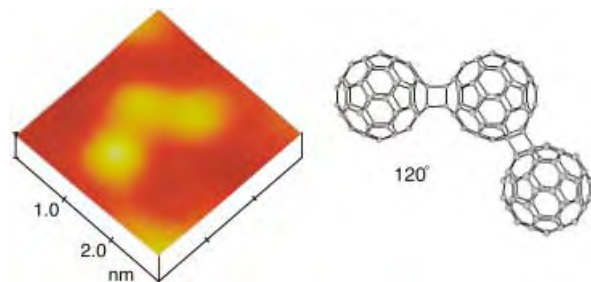
M. D. Hollingsworth,* M. E. Brown, M. Dudley, H. Chung, M. L. Peterson, A. C. Hillier 965–969

Template Effects, Asymmetry, and Twinning in Helical Inclusion Compounds

Keywords: chirality • helical structures • inclusion compounds • polymorphism • X-ray diffraction

Angew. Chem. **2002**, *114*, 1007–1011

Isomeric fullerene trimers have been prepared by using a high speed vibration milling technique, and Langmuir films of the isomers observed on Au(111) surfaces by scanning tunneling microscopy (STM). Each isomer exhibited a different surface morphology. The observed distribution of isomers supports molecular orbital calculations of isomer stability. STM may be used to distinguish the individual isomers (see image), which is difficult to achieve by spectroscopy.



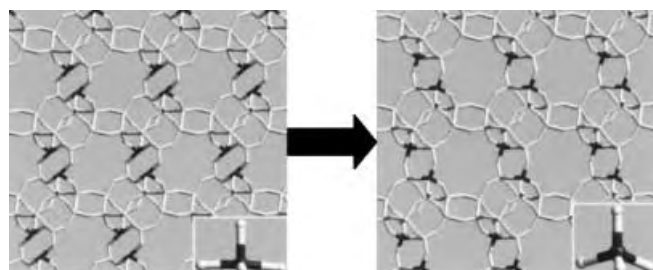
M. Kunitake,* S. Uemura, O. Ito, K. Fujiwara, Y. Murata, K. Komatsu* 969–972

Structural Analysis of C₆₀ Trimers by Direct Observation with Scanning Tunneling Microscopy

Keywords: fullerenes • nanotechnology • oligomers • scanning tunneling microscopy • solid-state reactions

Angew. Chem. **2002**, *114*, 1011–1014

Computer calcination: The phase transformation of two as-synthesized fluorinated inorganic compounds into their related microporous structures upon calcination (see scheme) is predicted by using lattice energy minimizations, successfully capturing in one step dehydration, defluorination, and template elimination.



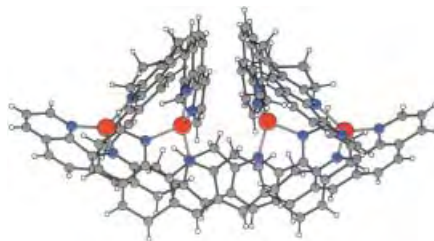
S. Girard, A. Tuel, C. Mellot-Draznieks, G. Férey* 972–975

Computational Prediction of the Phase Transformation of Two As-Synthesized Oxyfluorinated Compounds into the Zeotype CHA Forms

Keywords: aluminum • calcination • computer chemistry • microporous materials • zeolites

Angew. Chem. **2002**, *114*, 1014–1017

Anthracene in a bucket: Coordination-driven assembly of a ditopic ligand with copper salts leads to two stable tetranuclear complexes. The major complex, characterized by X-ray crystallography (see picture), displays a face-to-face arrangement of the phenanthroline subunits, and the inclusion of an anthracene molecule can be demonstrated by both proton NMR spectroscopy and cyclic voltammetry. The minor species has a plaited structure and does not exhibit significant interaction with the anthracene guest.



R. Ziessel,* L. Charbonnière, M. Cesario, T. Prangé, H. Nierengarten 975–979

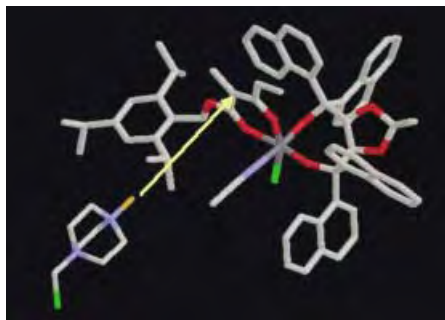
Assembly of a Face-to-Face Tetranuclear Copper(I) Complex as a Host for an Anthracene Guest

Keywords: copper • electrochemistry • host–guest systems • N ligands

Angew. Chem. **2002**, *114*, 1017–1021

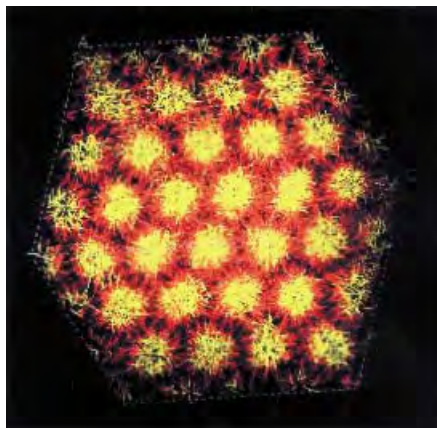


A parallel orientation between the coordinated substrate enolate and a face-on naphthyl group of the TADDOL ligand (see picture; Ti dark gray, O red, Cl green, F orange, N violet) control the stereochemical outcome of the Ti-catalyzed asymmetric fluorination of 1,3-dicarbonyl compounds with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanetriethylenediamine (F-TEDA; its approach is also shown in the picture). Density functional theory based quantum-mechanical molecular mechanical calculations also disclose the fluorine-transfer step as occurring by a single-electron transfer.



Angew. Chem. **2002**, *114*, 1021–1024

Aggregation without aggravation: A rapid and accurate estimation of the phase structure of amphiphilic molecules is made possible with a new computer simulation technique that excellently reproduces the aggregation behavior of such compounds. For dodecyldimethylamine oxide it is demonstrated how the micellar, hexagonal (see picture for isodensity profile), and lamella surfactant mesostructures can be calculated.



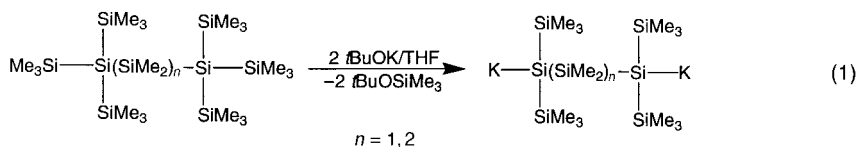
Angew. Chem. **2002**, *114*, 1025–1028

Industrial reaction improved: The first monocarbenepalladium(0)–olefin complex has been isolated and characterized (see structure; Pd orange, N green, S yellow, O blue). The complex exhibited unprecedented high catalyst productivity and selectivity for industrially important telomerization reactions (the dimerization of 1,3-dienes in the presence of a nucleophile, in this case an alcohol).



Angew. Chem. **2002**, *114*, 1028–1031

Multiply metalated oligosilanes: Treatment of bridged bis[tris(trimethylsilyl)silyl] compounds with two equivalents of potassium *tert*-butoxide leads to the formation of 1,3- and 1,4-dipotassium silanes [Eq. (1)]. Reaction of the latter with zirconocene dichloride and hafnocene dichloride, respectively, gives the corresponding metallocyclopentasilanes.



Angew. Chem. **2002**, *114*, 1031–1034

S. Piana, I. Devillers, A. Togni,*
U. Rothlisberger* 979–982

The Mechanism of Catalytic
Enantioselective Fluorination:
Computational and Experimental Studies

Keywords: density functional
calculations • electron transfer •
fluorination • TADDOLs • titanium

E. Ryjkina, H. Kuhn,* H. Rehage,
F. Müller, J. Peggau 983–986

Molecular Dynamic Computer
Simulations of Phase Behavior of
Non-Ionic Surfactants

Keywords: amphiphiles • colloids •
computer chemistry • micelles •
molecular modeling

R. Jackstell, M. Gómez Andreu,
A. Frisch, K. Selvakumar, A. Zapf,
H. Klein, A. Spannenberg, D. Röttger,
O. Briel, R. Karch, M. Beller* 986–989

A Highly Efficient Catalyst for the
Telomerization of 1,3-Dienes with
Alcohols: First Synthesis of a
Monocarbenepalladium(0)–Olefin
Complex

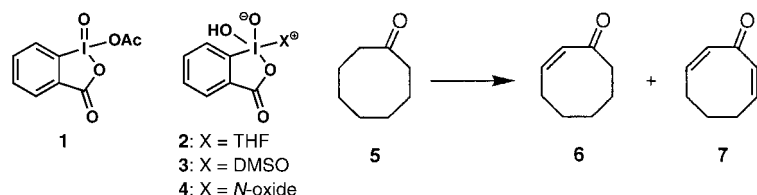
Keywords: carbene ligands •
homogeneous catalysis • palladium •
telomerization

C. Kayser, G. Kickelbick,
C. Marschner* 989–992

Simple Synthesis of Oligosilyl- α,ω -
dipotassium Compounds

Keywords: dianions • silanes •
Si ligands • silyl anions

The reactivity profile of IBX can be altered by complexation with various ligands (e.g. **1–4**). A new complex, IBX·MPO, is a remarkably effective oxidant and allows the room-temperature dehydrogenation of carbonyl compounds, for example, the formation of cyclooctenones **6** and **7** from cyclooctanone **5**. IBX = iodoxybenzoic acid; MPO = 4-methoxypyridine-*N*-oxide.



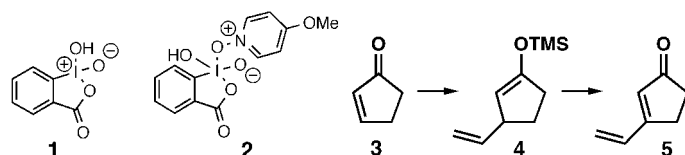
Angew. Chem. **2002**, *114*, 1035–1038

K. C. Nicolaou,* T. Montagnon,
P. S. Baran 993–996

Modulation of the Reactivity Profile of IBX by Ligand Complexation: Ambient Temperature Dehydrogenation of Aldehydes and Ketones to α,β -Unsaturated Carbonyl Compounds

Keywords: dehydrogenation • enones • hypervalent compounds • iodine • oxidation • synthetic methods

α,β -Unsaturated carbonyl compounds can be prepared by the oxidation of trimethylsilyl enol ethers with IBX (**1**) or IBX·MPO (**2**). A diverse set of carbonyl compounds can be dehydrogenated with ease by using this method. Trimethylsilyl enol ethers such as **4**, which are formed in situ with the addition of an organometallic species to an enone, can be dehydrogenated with **1** or **2** to give a functionalized enone (e.g. **3** → **5**). IBX = iodoxybenzoic acid; MPO = 4-methoxypyridine-*N*-oxide.



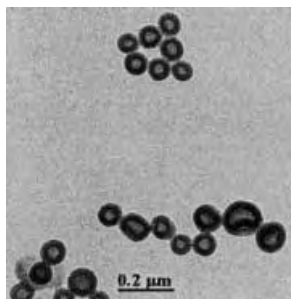
Angew. Chem. **2002**, *114*, 1038–1042

K. C. Nicolaou,* D. L. F. Gray,
T. Montagnon, S. T. Harrison . 996–1000

Oxidation of Silyl Enol Ethers by Using IBX and IBX·*N*-Oxide Complexes: A Mild and Selective Reaction for the Synthesis of Enones

Keywords: dehydrogenation • enols • hypervalent compounds • iodine • oxidation • synthetic methods

By varying the hydrophilic block lengths in polystyrene diblock copolymers containing both polystyrene-*b*-poly(acrylic acid) (PS-*b*-PAA) and polystyrene-*b*-poly(4-vinylpyridine) (PS-*b*-P(4-VP)), vesicles can be prepared (see transmission electron micrograph) in which the PAA and P(4-VP) chains can be preferentially segregated on the inside and outside of the vesicles.



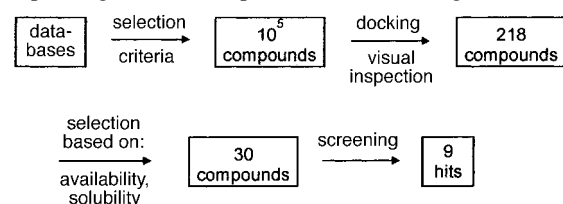
Angew. Chem. **2002**, *114*, 1043–1046

L. Luo, A. Eisenberg* 1001–1004

One-Step Preparation of Block Copolymer Vesicles with Preferentially Segregated Acidic and Basic Corona Chains

Keywords: block copolymers • colloids • curvature stabilization • electron microscopy • vesicles

Molecular docking with a large number of guests, followed by experimental verification, was used to determine the selectivity of a synthetic host molecule and resulted in a hit rate of 30% (see schematic outline of procedure). The identification of ligands for a given receptor by means of screening may represent a paradigm shift in supramolecular host–guest chemistry.



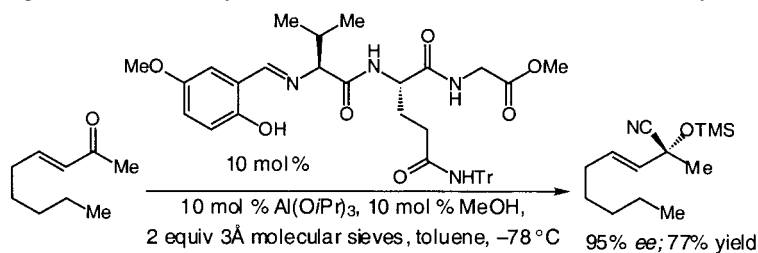
Angew. Chem. **2002**, *114*, 1046–1050

M. R. de Jong, R. M. A. Knegtel,
P. D. J. Grootenhuys, J. Huskens,*
D. N. Reinhoudt* 1004–1008

A Method To Identify and Screen Libraries of Guests That Complex to a Synthetic Host

Keywords: computer chemistry • cyclodextrins • fluorescence spectroscopy • host–guest systems • screening

Easily prepared peptide-based ligands efficiently promote the Al-catalyzed enantioselective addition of trimethylsilyl cyanide (TMSCN) to aromatic, aliphatic, cyclic, and acyclic ketones (see scheme for an example). The chiral ligands can be readily recovered and reused without loss of activity or selectivity.



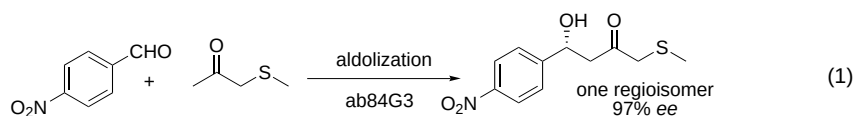
Angew. Chem. **2002**, *114*, 1051–1054

H. Deng, M. P. Isler, M. L. Snapper,*
A. H. Hoveyda* 1009–1012

Aluminum-Catalyzed Asymmetric Addition of TMSCN to Aromatic and Aliphatic Ketones Promoted by an Easily Accessible and Recyclable Peptide Ligand

Keywords: addition • aluminum • asymmetric catalysis • asymmetric synthesis • cyanohydrins

Direct asymmetric aldol reactions at the less substituted carbon atom of unmodified unsymmetrical ketones are achieved in the presence of the commercially available aldolase I antibody 84G3 [Eq. (1)]. All the reactions proceeded with enantiomeric excesses greater than 94 %. Both enantiomers are accessible by using either an aldol or a retro-aldol reaction.



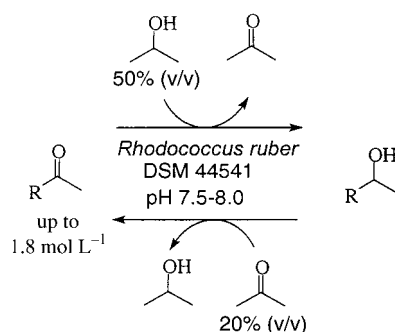
Angew. Chem. **2002**, *114*, 1054–1056

V. Maggiotti, M. Resmini,
V. Gouverneur* 1012–1014

Unprecedented Regiocontrol Using An Aldolase I Antibody

Keywords: aldol reaction • asymmetric catalysis • catalytic antibodies • regioselectivity

Celling chemistry: Ketones (secondary alcohols) can be biocatalytically reduced (oxidized) at a substrate concentration of up to 1.8 mol L⁻¹ in an asymmetric fashion by employing a novel secondary alcohol dehydrogenase from *Rhodococcus ruber* DSM 44541 (see scheme). Furthermore, the enzyme is exceptionally stable at high co-substrate concentrations, that is, 2-propanol (50 % v/v) for reduction and acetone (20 % v/v) for oxidation, respectively.



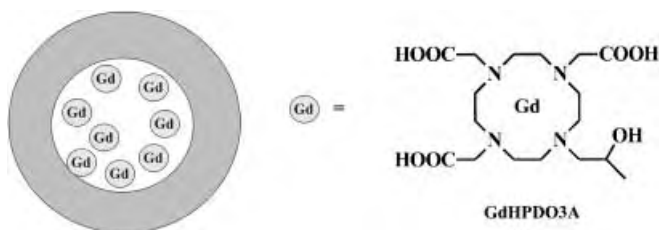
Angew. Chem. **2002**, *114*, 1056–1059

W. Stampfer, B. Kosjek, C. Moitzi,
W. Kroutil,* K. Faber 1014–1017

Biocatalytic Asymmetric Hydrogen Transfer

Keywords: alcohols • biocatalysis • enzyme catalysis • hydrogen transfer • oxidoreductases

A remarkably high relaxation enhancement of water protons has been observed for solutions containing apoferritin loaded with GdHPDO3A (see schematic representation). The entrapment of the complex within apoferritin (internal diameter: 7.5 nm, external diameter: 12.5 nm) allows an increased number of dipolar interactions with water molecules and exchangeable protons in the protein cavity.



Angew. Chem. **2002**, *114*, 1059–1061

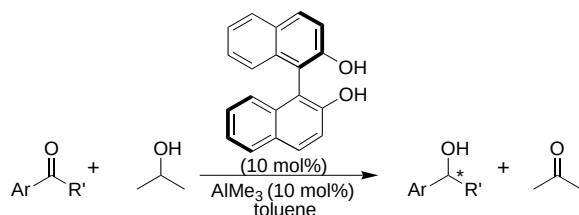
S. Aime,* L. Frullano,
S. Geninatti Crich 1017–1019

Compartmentalization of a Gadolinium Complex in the Apoferritin Cavity: A Route To Obtain High Relaxivity Contrast Agents for Magnetic Resonance Imaging

Keywords: apoferritin • contrast agents • lanthanides • magnetic resonance imaging • relaxivity



Efficient and practical: An aluminum-based catalyst system for the asymmetric Meerwein–Schmidt–Ponndorf–Verley reduction of aromatic ketones is reported. By using *i*PrOH as the achiral hydride source and BINOL-type chiral ligands (see scheme), chiral secondary aromatic alcohols (up to 83 % *ee*) can be obtained in good yields.



Angew. Chem. **2002**, *114*, 1062–1064

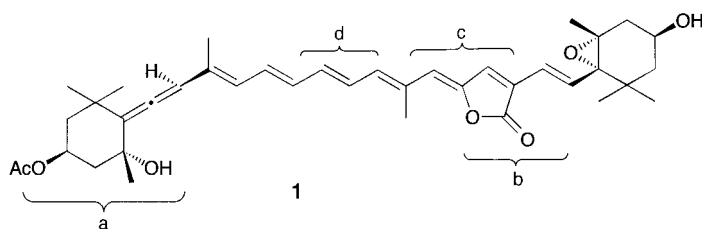
E. J. Campbell, H. Zhou,
S. T. Nguyen* 1020–1022

The Asymmetric Meerwein–Schmidt–Ponndorf–Verley Reduction of Prochiral Ketones with *i*PrOH Catalyzed by Al Catalysts

Keywords: aluminum • asymmetric synthesis • homogeneous catalysis • ketones • reduction



The convergent, highly stereoselective synthesis of the nor carotenoid peridinin (**1**) is based on the following key steps: a) a Sharpless asymmetric epoxidation, b) reaction with a silylfuran–Wittig reagent and oxidation with $^1\text{O}_2$, c) a Pd-catalyzed three-step one-pot procedure for the formation of the ylidene butenolide segment), and d) a modified Julia olefination. This provides a new method for the synthesis of carotenoids.



Angew. Chem. **2002**, *114*, 1065–1068

N. Furuichi, H. Hara, T. Osaki, H. Mori,
S. Katsumura* 1023–1026

Highly Efficient Stereocontrolled Total Synthesis of the Polyfunctional Carotenoid Peridinin

Keywords: asymmetric synthesis • carotenoids • diastereoselectivity • synthetic methods • total synthesis



A deep hole trap is 7-deazaguanine (Z)—according to time-resolved transient absorption spectroscopy and kinetic modeling—for hole transport in DNA from a guanine (G) to a Z base across one or two intervening adenine–thymine base pairs. The Gibbs energy for hole transport from G to Z was determined to be -0.19 eV, much larger than values for GG or GGG sites. Thus Z effectively prevents charge migration in DNA.

Angew. Chem. **2002**, *114*, 1068–1070

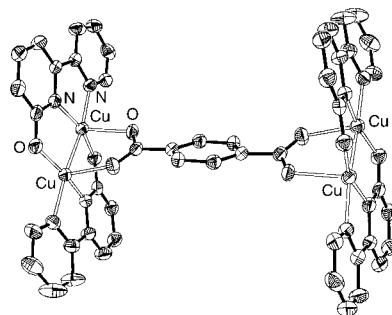
F. D. Lewis,* J. Liu, X. Liu, X. Zuo,
R. T. Hayes,
M. R. Wasielewski* 1026–1028

Dynamics and Energetics of Hole Trapping in DNA by 7-Deazaguanine

Keywords: DNA conjugates • electron transfer • photooxidation • picosecond spectroscopy

Structural evidence for the Gillard mechanism of covalent hydrates is provided by two mixed-valence $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ complexes containing 2,2'-bipyridine (see picture) or 1,10-phenanthroline ligands, in which a hydroxy group is added to a carbon atom adjacent to a nitrogen atom. These complexes are synthesized by hydrothermal treatment of $\text{Cu}(\text{NO}_3)_2$, the respective N,N ligand, and terephthalic acid.

Angew. Chem. **2002**, *114*, 1071–1073

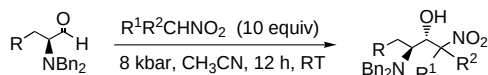


X.-M. Zhang, M.-L. Tong,
X.-M. Chen* 1029–1031

Hydroxylation of N-Heterocycle Ligands Observed in Two Unusual Mixed-Valence $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ Complexes

Keywords: copper • hydroxylation • mixed-valent compounds • N ligands • reaction mechanisms

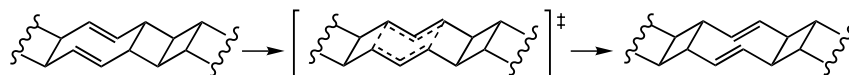
Under pressure, the nitro-aldol reaction of (*S*)-*N,N*-dibenzylphenylalaninal and related compounds with nitroalkanes was highly stereoselective (see scheme; R^1 , R^2 = Me, H; R = Ph, Me, *i*Pr, *i*Bu). This reaction is very convenient, as it only requires high pressure and no catalyst.



Angew. Chem. **2002**, *114*, 1073–1075

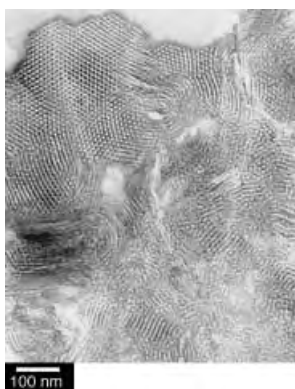


A new (and so far hypothetical) class of molecules is described—the “sigmatropic shiftamers.” These are polymers that contain local “defects”—single or double bonds—which propagate by sigmatropic rearrangements (see scheme).



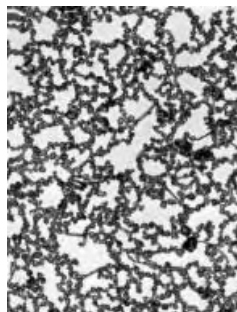
Angew. Chem. **2002**, *114*, 1075–1078

A uniform pore size with a highly ordered structure is still observed for zeolite (ZSM-5)-coated mesoporous aluminosilicates (ZCMesoAS) even after the coating procedure (see transmission electron micrograph). These ZCMesoAS, which are hydrothermally ultrastable and highly acidic owing to the nanocrystalline zeolitic nature of their pore wall surface, are produced from diluted clear solutions containing primary zeolite units. The novel features of ZCMesoAS open new possibilities for their use as acid catalysts.



Angew. Chem. **2002**, *114*, 1078–1082

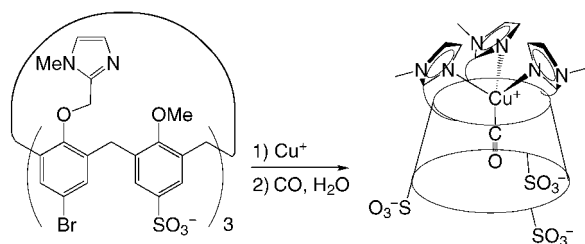
The concentration of the plating solution enables control over the fine-tuning of fractal patterns and also drastically affects the crystal growth of Ag/Au core–shell roughened nanoparticles through diffusion-limited aggregation. At low concentrations there are more open spaces in the well-ramified fractal pattern than at higher concentrations, and the whisker-linked nanoparticles align almost one-by-one (see transmission electron micrograph).



Angew. Chem. **2002**, *114*, 1082–1086



Remarkable stabilization of a copper(I) center is evident in the tris(sulfonated) calixarene-based complex shown. This complex is truly biomimetic as it is soluble in water and also has a free valence where CO can bind. Thus it imitates the first coordination sphere encountered in copper enzymes and the hydrophobic microenvironment of the active site.



Angew. Chem. **2002**, *114*, 1086–1088

Y. Misumi, K. Matsumoto* . 1031–1033

Diastereoselective Asymmetric Nitro-Aldol Reaction of α -Amino Aldehydes under High Pressure without Catalyst

Keywords: addition • amino alcohols • asymmetric synthesis • diastereoselectivity • high-pressure chemistry • synthetic methods

D. J. Tantillo, R. Hoffmann* . 1033–1036

Sigmatropic Shiftamers: Fluxionality in Broken Ladderane Polymers

Keywords: Cope rearrangement • ladderanes • polymers • rearrangement • transition states

D. Trong On, S. Kaliaguine* . 1036–1040

Ultrastable and Highly Acidic, Zeolite-Coated Mesoporous Aluminosilicates

Keywords: mesoporous materials • nanostructures • solid-state reactions • zeolites

Y. Jin, S. Dong* 1040–1044

Diffusion-Limited, Aggregation-Based, Mesoscopic Assembly of Roughened Core-Shell Bimetallic Nanoparticles into Fractal Networks at the Air-Water Interface

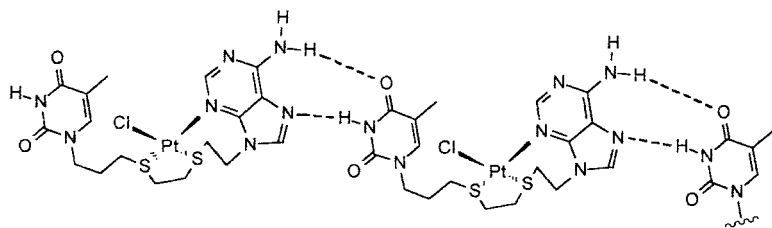
Keywords: aggregation • electron microscopy • fractals • nanoparticles

Y. Rondelez, G. Bertho, O. Reinaud* 1044–1046

The First Water-Soluble Copper(I) Calix[6]arene Complex Presenting a Hydrophobic Ligand Binding Pocket: A Remarkable Model for Active Sites in Metalloenzymes

Keywords: calixarenes • copper • enzyme models • host–guest systems • solvent effects

Hoogsteen base pairing between coordinated adenine (A) and pendant thymine (T) residues of the Pt complex of a dithioether ligand bearing A and T groups results in the formation of infinite chains in the solid state (see picture). The chains are further involved in π - π stacking interactions.



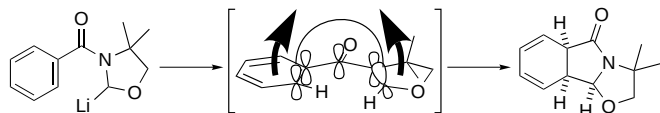
Angew. Chem. **2002**, *114*, 1089–1091

C. Price, B. R. Horrocks, A. Mayeux,
M. R. J. Elsegood, W. Clegg,
A. Houlton* 1047–1049

Self-Complementary Metal Complexes
Containing a DNA Base Pair

Keywords: chain structures • hydrogen
bonds • nucleobases • self-assembly •
S ligands

Loss of aromaticity ensues when *N*-benzoyl oxazolidines are lithiated and undergo a 6π disrotatory electrocyclic ring closure (see scheme). The stereochemistry of the cyclization shows it to be a new example of an electrocyclic ring closure. The *cis*-tricyclic products epimerize to their more stable *trans* diastereoisomers in aqueous acid.



Angew. Chem. **2002**, *114*, 1091–1093

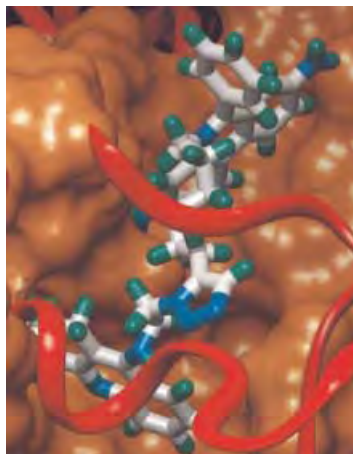
J. Clayden,* S. Purewal, M. Helliwell,
S. J. Mantell 1049–1051

Dearomatizing Disrotatory Electrocyclic
Ring Closure of Lithiated
N-Benzoyloxazolidines

Keywords: amides • cyclization •
lithiation • pericyclic reaction •
stereoselectivity



Form-fitting chemistry in a protein mold is enabled by the use of the 1,3-dipolar cycloaddition of azides and alkynes. The enzyme acetylcholinesterase preferentially assembles one pair of these reactants, each of which bears a group that binds to adjacent positions on the protein structure (see picture), into a 1,2,3-triazole adduct that is the most potent noncovalent inhibitor of the enzyme yet developed.



Angew. Chem. **2002**, *114*, 1095–1098

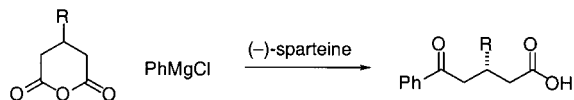
W. G. Lewis, L. G. Green, F. Grynszpan,
Z. Radić, P. R. Carlier,
P. Taylor, M. G. Finn,*
K. B. Sharpless* 1053–1057

Click Chemistry In Situ:
Acetylcholinesterase as a Reaction Vessel
for the Selective Assembly of a
Femtomolar Inhibitor from an Array of
Building Blocks

Keywords: combinatorial chemistry •
cycloaddition • heterocycles •
hydrolases • inhibitors



Where other common chiral ligands failed, (–)-sparteine can be employed to form complexes with Grignard reagents. These chirally modified reagents desymmetrize a range of anhydrides with good enantioselectivity (up to 92% *ee*; see scheme). Whereas (–)-sparteine is well known to form complexes with organolithium reagents and to induce excellent enantioselection in their reactions with electrophiles, (–)-sparteine-controlled asymmetric processes that involve Grignard reagents are rare.



Angew. Chem. **2002**, *114*, 1099–1101

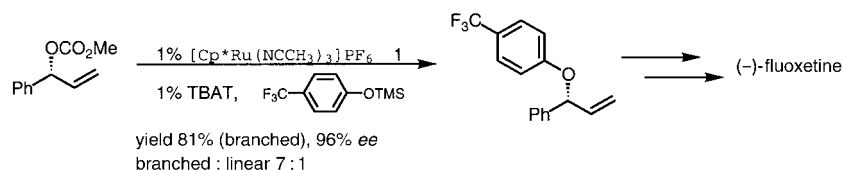
R. Shintani, G. C. Fu* 1057–1059

Highly Enantioselective
Desymmetrization of Anhydrides by
Carbon Nucleophiles: Reactions of
Grignard Reagents in the Presence of
(–)-Sparteine

Keywords: anhydrides • asymmetric
synthesis • desymmetrization • Grignard
reaction



Good regioselectivity and chirality transfer for aryl-substituted allyl units is achieved in allylic alkylations with a wide range of nucleophiles by using the highly active ruthenium catalyst **1**. This method provides a route to antidepressants such as (–)-fluoxetine from (S)-ephedrine (see scheme; Cp* = η^5 -C₅Me₅, TBAT = tetrabutylammonium triphenyldifluorosilicate).



Angew. Chem. **2002**, *114*, 1101–1103

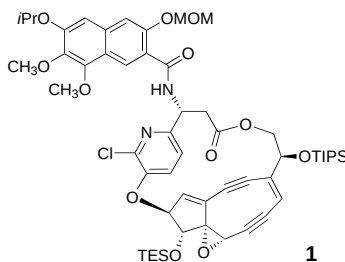
B. M. Trost,* P. L. Fraise,
Z. T. Ball 1059–1061

A Stereospecific Ruthenium-Catalyzed
Allylic Alkylation

Keywords: alkylation • allylic
compounds • chirality transfer •
homogeneous catalysis • regioselectivity •
ruthenium



Four components, each prepared in multigram amounts, have been assembled in the convergent (25 steps in the longest linear sequence), enantioselective synthesis of the differentially protected kedarcidin chromophore aglycon (**1**). In addition to the enantioselective synthesis of each of the four components, the route features a transannular anionic cyclization to form the bicyclo[7.3.0]dodecadienediyne core in the presence of an ansa-bridged macrolactone. MOM = methoxymethyl, TIPS = triisopropylsilyl, TES = triethylsilyl.



A. G. Myers,* P. C. Hogan, A. R. Hurd,
S. D. Goldberg 1062–1067

Enantioselective Synthesis of Kedarcidin
Chromophore Aglycon in Differentially
Protected Form

Keywords: aglycons • antibiotics •
asymmetric synthesis • cyclization •
enediynes

Angew. Chem. **2002**, *114*, 1104–1109



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* Author to whom correspondence should be addressed



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This issue contains as a supplement an index of all the reviews published in *Angewandte Chemie* between 1962 and 2001.



Dynamic Covalent Chemistry

Stuart J. Rowan,* Stuart J. Cantrill, Graham R. L. Cousins, Jeremy K. M. Sanders, and J. Fraser Stoddart

In memory of Donald J. Cram

Dynamic covalent chemistry relates to chemical reactions carried out reversibly under conditions of equilibrium control. The reversible nature of the reactions introduces the prospects of “error checking” and “proof-reading” into synthetic processes where dynamic covalent chemistry operates. Since the formation of products occurs under thermodynamic control, product distributions depend only on the relative stabilities of the final products. In kinetically controlled reactions, however, it is the free energy differences between the transition states leading to the products that determines their relative proportions. Supramolecular chemistry has had a huge impact on synthesis at two levels: one is non-covalent synthesis, or strict self-assembly, and the other is supramolecular assistance to molecular synthesis, also referred to as self-assembly followed by covalent modification. Noncovalent

synthesis has given us access to finite supermolecules and infinite supramolecular arrays. Supramolecular assistance to covalent synthesis has been exploited in the construction of more-complex systems, such as interlocked molecular compounds (for example, catenanes and rotaxanes) as well as container molecules (molecular capsules). The appealing prospect of also synthesizing these types of compounds with complex molecular architectures using reversible covalent bond forming chemistry has led to the development of dynamic covalent chemistry. Historically, dynamic covalent chemistry has played a central role in the development of conformational analysis by opening up the possibility to be able to equilibrate configurational isomers, sometimes with base (for example, esters) and sometimes with acid (for example, acetals). These stereochemical “balancing acts” revealed another

major advantage that dynamic covalent chemistry offers the chemist, which is not so easily accessible in the kinetically controlled regime: the ability to re-adjust the product distribution of a reaction, even once the initial products have been formed, by changing the reaction’s environment (for example, concentration, temperature, presence or absence of a template). This highly transparent, yet tremendously subtle, characteristic of dynamic covalent chemistry has led to key discoveries in polymer chemistry. In this review, some recent examples where dynamic covalent chemistry has been demonstrated are shown to emphasise the basic concepts of this area of science.

Keywords: catenanes • combinatorial chemistry • macrocycles • polymers • rotaxanes • supramolecular chemistry

1. Background

The molecular synthesis of organic compounds has been dominated^[1] traditionally by kinetically controlled reactions,

[*] Prof. S. J. Rowan

Department of Macromolecular Science
Case Western Reserve University
2100 Adelbert Road, Cleveland, OH 44106-7202 (USA)
Fax: (+1) 216-368-4202
E-mail: sjr4@po.cwru.edu

Dr. S. J. Cantrill, Prof. J. F. Stoddart
Department of Chemistry and Biochemistry
University of California, Los Angeles
405 Hilgard Avenue, Los Angeles, CA 90095-1569 (USA)

Dr. G. R. L. Cousins, Prof. J. K. M. Sanders
University Chemical Laboratory
Lensfield Road, Cambridge, CB2 1EW (UK)

which result in the irreversible formation of (strong) covalent bonds. In this kind of synthetic chemistry, reagents (or catalysts) and conditions are chosen very carefully for the efficient production of a single product. In essence, a more favorable energetic pathway to the formation of a particular product, rather than other possible products, is usually the objective, for example, **A** goes to **C** rather than to **B** in Figure 1. The irreversible nature of the reaction guarantees that, once the particular product is formed, it is not possible either for the starting materials to be reformed from it or for it to be converted into another product (at least under the conditions of the reaction). In this manner, chemists have historically devised efficient syntheses of both natural and unnatural products.^[2] Recently, however, there has been a resurgence of interest in a branch of chemistry where the covalent bond has the ability to be formed and broken, and



S. J. Rowan



S. J. Cantrill



G. R. L. Cousins



J. K. M. Sanders



J. F. Stoddart

Stuart J. Rowan was born in Edinburgh, Scotland in 1969. He received his B.Sc. in 1991 from the University of Glasgow. He stayed at Glasgow for his Ph.D. where he worked on "Supramolecular Crystal Engineering of Inclusion Compounds" in the laboratories of Dr. David D. MacNicol, and received his Ph.D. in 1995. In 1994 he moved to Cambridge to work with Prof. Jeremy K. M. Sanders. There he carried out research on the development of dynamic combinatorial libraries focusing on the transesterification reaction. In 1996 he was appointed a Research Associate of Girton College, Cambridge. In 1998 he moved to the University of California, Los Angeles (USA) to continue his postdoctoral studies with Prof. J. Fraser Stoddart. Here, he developed numerous new methods for the construction of interlocked species, specifically using dynamic covalent chemistry and "surrogate" stoppers. In 1999 he was appointed as an Assistant Professor to the Department of Macromolecular Science at Case Western Reserve University in Cleveland, Ohio. His research interests focus on the potential of dynamic chemistry (covalent and noncovalent) in the construction and properties of polymeric materials and developing new synthetic methods for the construction of complex polymeric architectures.

Stuart J. Cantrill was born in Lichfield, England in 1974. In 1993 he embarked upon a study of Chemistry and Bioorganic Chemistry at the University of Birmingham which culminated in the award of his B.Sc. degree in 1996. Thereafter, he remained in Birmingham and began his Ph.D. studies in the laboratories of Prof. J. Fraser Stoddart. One year later, after receiving his M.Phil. degree, however, he moved to the University of California, Los Angeles, with Professor J. F. Stoddart where in 2001 he completed his Ph.D. degree on the interaction between secondary dialkylammonium ions and crown ethers, particularly concerning self-complementary "daisy chain" systems. He is currently a postdoctoral researcher at the California Institute of Technology, working in the research group of Prof. Robert H. Grubbs.

Graham Cousins was born in Southampton (UK) in 1975. He obtained his B.Sc. in Chemistry in 1997 from the University of Birmingham (UK). He moved to Cambridge (UK) to join the group of Jeremy Sanders and was awarded his Ph.D. in 2000. His primary research interests are in the fields of Supramolecular Chemistry and Combinatorial Chemistry. At Birmingham he conducted undergraduate research projects in the group of Prof. J. Fraser Stoddart exploring the use of crown ether/ammonium center recognition to synthesize rotaxane-based molecular switches. His Ph.D. thesis titled "Dynamic Combinatorial Libraries of Hydrazone Based Pseudo-peptides: Diversity, Templating and Selection" was concerned with the generation of dynamic combinatorial libraries using hydrazone chemistry and the subsequent amplification and selection of receptors using supramolecular interactions with template molecules.

Jeremy Sanders was born in London in 1948, and obtained his B.Sc. from Imperial College, London, in 1969. He moved to Cambridge to work for his Ph.D. with Prof. Dudley Williams on lanthanide shift reagents. After a postdoctoral year (1972–1973) in the USA, working on protein NMR spectroscopy, he joined the staff of the University of Cambridge; he was appointed to his present Chair in 1996, and became Head of the Department of Chemistry in October 2000. He is also Chairman of the Editorial Board of Chemical Society Reviews. A sabbatical year (1979–1980) at the University of British Columbia with Professor Laurie Hall, showing how two-dimensional NMR and NOE difference spectroscopy could dramatically enhance the value of NMR for chemists, led to his writing the book "Modern NMR Spectroscopy" with Brian Hunter. His interests in NMR spectroscopy have covered such diverse topics as drug metabolism in live cells and the biophysics of biodegradable plastics and spiders' webs. His major research interest is in molecular recognition and supramolecular chemistry, embracing the synthesis of organic and inorganic systems, and the development of analytical methods for studying them. He is particularly well known for templated syntheses of receptors based on metalloporphyrins, for studies of molecular recognition by metalloporphyrins, and for the recent development of the concept of dynamic combinatorial chemistry. He was elected a Fellow of the Royal Society in 1995, one year after J. Fraser Stoddart.

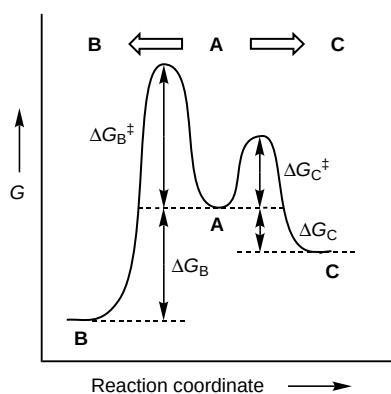


Figure 1. Free energy profile illustrating kinetic ($A \rightarrow C$) versus thermodynamic ($A \rightarrow B$) control of the product distribution. Most covalent chemistry is irreversible and so occurs under kinetic control while most supramolecular and dynamic covalent chemistry is reversible and so occurs under thermodynamic control.

indeed reformed, reversibly under equilibrium control.^[3] If the equilibration process is sufficiently fast, then this so-called dynamic covalent chemistry leads to the efficient formation of products under thermodynamic control, for example, **A** gives **B** rather than **C** (Figure 1). In such reactions, it is the relative stabilities of the resulting products (ΔG_B° compared with ΔG_C° in Figure 1) and not the relative magnitudes ($\Delta G_B^\ddagger$ versus $\Delta G_C^\ddagger$) of the transition states to the different products (**B** and **C**) that controls the proportions of the products. Thus, we can control the proportions of the products in dynamic chemical systems simply by 1) introducing certain features into either the starting materials (for example, constitutional, steric, and electronic effects that will stabilize the desired product and so encourage equilibration to the thermodynamically most stable product) and/or by 2) driving the reaction equilibrium toward the formation of the desired product by using, for example, an excess of one of the starting materials or removing a condensation product. In kinetically controlled reactions, chemists must build features into the substrates and/or reagents (and catalysts) which will stabilize the transition state that leads to the desired product. Therefore, we need a detailed understanding of the different transition

states en route to all the possible products to achieve a controlled product distribution in irreversible reactions.

The field of dynamic covalent chemistry is currently undergoing a revival, largely on account of our increased understanding of supramolecular phenomena and the subsequent development of self-assembly processes.^[4] Supramolecular chemistry—the discipline^[5] which is concerned with noncovalent interactions involving ions and molecules in complexes—is also dominated by thermodynamically controlled process^[6] and, as such, allows access to a vast and fascinating array of noncovalent superstructures.^[7] However, since many of these superstructures are not very stable, particularly in solution, they are often difficult to characterize and investigate further. Thus, the possibility of constructing molecular architectures with reversible structural elements at a more robust level is an extremely appealing one. Dynamic covalent chemistry has a lot of features in common with supramolecular chemistry; both involve bonding processes that are reversible and the formation of products that are in continuous equilibrium. These common characteristics result not only in the possibility of carrying out synthesis under thermodynamic control, but also in making it possible for the products to undergo “error-checking” or “proof-reading”—a process which ensures the eradication of thermodynamically unstable products.

There are, however, some major differences between these two distinct types of reversible systems. In general, the equilibration processes are much slower in dynamic covalent chemical systems than in supramolecular ones. This observation reflects the fact that covalent, rather than noncovalent, bonds have to be broken in the former. The slower kinetics associated with dynamic covalent bond forming reactions usually means that they require a catalyst to help the system to equilibrate to the thermodynamically stable product on a reasonable time scale. In fact, most of the appropriate dynamic covalent bonds are sufficiently strong that they do not undergo rupture and/or exchange without a catalyst being present. This underlying stability of many reversible bonds offers us the possibility of being able to “fix” kinetically the products simply by “quenching” the system in some appropriate manner—something that cannot be done in the case of

J. Fraser Stoddart was born in Edinburgh, Scotland in 1942. He received his B.Sc., Ph.D., and D.Sc. degrees in 1964, 1966, and 1980, respectively, from the University of Edinburgh. He carried out postdoctoral research at Queen's University, Canada for three years before joining the academic staff at the University of Sheffield in 1970. There he remained, aside from a highly informative and influential three-year (1978–1981) secondment to the ICI Corporate Laboratory in Runcorn, for 20 years. After seven years as the Professor of Organic Chemistry at the University of Birmingham, he moved to UCLA in 1997, to take up the Saul Winstein Chair of Organic Chemistry. He has published over 600 scientific papers and, according to the Institute for Scientific Information, is one of the 100 most-cited chemists in the world today for his research into the nature of noncovalent, dynamic covalent, and mechanical bonds going back over the past 30 years. By employing supramolecular assistance to covalent synthesis and, more recently, dynamic covalent bond forming reactions, he has been assembling molecular machinery based on redox-switchable catenanes and rotaxanes for almost 15 years. These unconventional routes to exotic molecules are being exploited currently in the construction of nanoelectromechanical systems (NEMS) and molecular electronic devices (MEDs). Very recent research, involving an integrated systems-oriented approach to molecular electronics, has resulted in the design and synthesis of amphiphilic, bistable [2]rotaxanes for use in the fabrication of memory and logic circuits for a chemical computer.

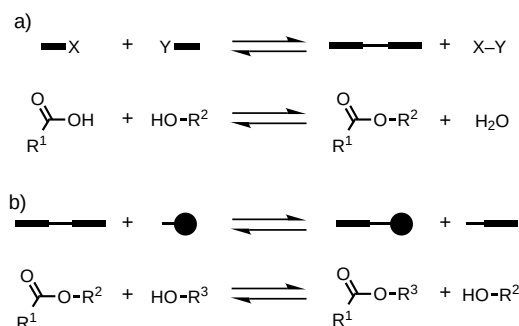
supramolecular systems.^[8] Finally, whereas supramolecular chemistry is concerned with the formation of noncovalently bound aggregates (supermolecules and supramolecular arrays) which tend to be fragile, dynamic covalent chemistry deals with the production of robust molecules.^[9]

For the dynamic reaction to proceed in the direction of the products, the change in free energy during the reaction must be favorable, that is ΔG° in Equation (1) is negative.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = -RT \ln K \quad (1)$$

It also means that a number of external factors, such as temperature, concentration, pressure, and impurities, can have a dramatic effect upon the equilibrium and so change the product distribution, even once the initial product has been formed. This adjustable set of parameters opens up the attractive possibility of being able to design and make molecules that can adapt to their surroundings.

There is a range of different dynamic covalent bonds that lend themselves to carrying out reactions on organic compounds under thermodynamic control. In general, reversible reactions, such as the two examples shown in Scheme 1, can be assigned to one of two different categories: a) making/breaking of the reversible bond, where the reversible process



Scheme 1. Two possible types of reversible reaction: a) involving the formation/scission of a new type of bond (for example, ester formation/cleavage) and b) involving a direct exchange reaction (for example, transesterification).

involves formation/scission of one type of bond from/to another in a mechanism that involves the generation of a condensation product with loss of a small molecule; an example is the reaction of a carboxylic acid and an alcohol to yield an ester and water (Scheme 1a), and b) a direct exchange reaction where the reversible covalent bond is of the same type in both starting material and product; an example is transesterification (Scheme 1b) wherein an ester and an alcohol are in equilibrium with a different ester and alcohol. Energetically, these processes are different. Transesterification is almost energetically “neutral” on account of the fact that the same number and types of bonds are present in both the reactants and the products. However, in the case of ester formation, there is a slight driving force, which is reflected in a typical equilibrium constant of $K = 1 - 10 \text{ M}^{-1}$ for the formation of the more stable ester.^[10] Other examples^[3] of potentially dynamic covalent functionalities include acetals, borazaaromatic anhydrides, borate esters, disulfides, hydra-

zones, imines, oximes, and olefins (metathesis). The formation of most of these functional groups requires a catalyst to initialize and/or speed up the appropriate equilibration. The type of catalyst that is used depends on the nature of the covalent bond that it is required to render “dynamic”. Even stable covalent bonds, such as ethers and amides, can be made reversible, for example, in some polymerizations. However, the catalysts and conditions required to establish the equilibria are usually much too harsh to tolerate the presence of other functionalities in the molecule. In this review, we shall concentrate on dynamic covalent bonds that have the potential to become reversible under relatively mild conditions. Moreover, we will focus on those contemporary areas of research which have been influenced most by the development of reversible chemistry, and highlight particular types of dynamic covalent bonds.

2. Equilibrium (Dynamic) Polymerizations

One of the oldest and most investigated fields in which dynamic covalent chemistry has played an important role is polymer synthesis. Equilibrium (or dynamic) polymerizations^[11] have been known for sometime for a range of different types of monomers, including vinyl compounds (for example, methyl methacrylate^[12]), aldehydes (for example, chloral^[13]), cyclic ethers (for example, THF^[14]), cyclic acetals (for example, 1,3-dioxolane^[15]), cyclic esters (for example, lactide^[16]), cyclic amides (for example, ϵ -caprolactam^[17]), and inorganic compounds (for example, sulfur^[18] or octamethylcyclotetrasiloxane^[19]).

Dynamic polymerizations potentially offer a number of key differences to those of irreversible polymerizations. If the system is truly reversible—which may require the presence of a catalyst—then the material can be responsive to external stimuli. The system can, therefore, change its constitution depending on environmental considerations, such as temperature, pressure, presence of a template. This adaptability potentially offers the development of “smart” materials which can respond to their environment through the use of dynamic covalent chemistry. Furthermore, reversible polymerizations may also allow access to more complex, thermodynamically stable polymeric architectures. In our treatment of the topic we will concentrate on some recent developments in the area of equilibrium polymerizations and highlight the key concepts and general rules which cover most polymerizations carried out under thermodynamic control. Furthermore, most of the theory and concepts outlined also hold true for other types of dynamic synthesis, such as those used in the construction of macrocycles, complex architectures, and dynamic libraries.

For a polymerization to proceed under continuous equilibrium control then a few ideal conditions need to be fulfilled:

- 1) A certain concentration of active centers must be present continuously at equilibrium.
- 2) It is desirable that the reaction proceeds homogeneously and that the reaction mixture does not become too viscous.
- 3) It is essential that the system contains only monomers, oligomers, and polymers which are all interchangeable.
- 4) No irreversible side reactions occur.

Most polymerizations can be viewed as having three basic mechanistic steps: 1) initiation, 2) propagation, and 3) termination. However, there are a variety of possible ways in which dynamic covalent chemistry may be involved with these three basic steps during polymerizations.

2.1. Reversible Propagation

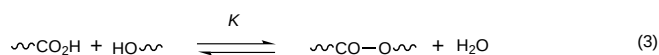
First of all, let us examine the simplest case of equilibrium polymerization where the only equilibrium step (Scheme 2a) is the propagation/depropagation one: the monomer/polymer equilibrium. This type of equilibrium polymerization is observed for a number of chain polymerizations, including the anionic polymerization^[20] of α -methylstyrene and the radical polymerization of 7-(alkoxycarbonyl)-7-cyano-1,4-benzoquinone methides. An analysis of the thermodynamics of the polymerization process^[21] leads to Equation (2) which describes the relationship between enthalpy, entropy, temperature, and the equilibrium monomer concentration $[M]_e$.

$$T = \Delta H^\circ / (\Delta S^\circ + R \ln[M]_e) \text{ or } \ln[M]_e = \Delta H^\circ / RT - \Delta S^\circ / R \quad (2)$$

Polymerization will only proceed if the initial monomer concentration $[M]_0$ is greater than $[M]_e$ and will only continue until the monomer concentration $[M]$ reaches the equilibrium monomer concentration $[M]_e$. Equation (2) indicates that, under standard conditions ($[M]_0 = 1\text{M}$), if the enthalpy of polymerization ΔH_p is < 0 and the entropy of polymerization ΔS_p is > 0 , then the monomer can be polymerized at any temperature. However, while most polymerizations are exothermic ($\Delta H_p < 0$), they are also exentropic ($\Delta S_p < 0$). When these thermodynamic characteristics hold, then for a given monomer concentration and solvent there will be a temperature above which formation of long chain polymer will not occur (that is $\Delta G^\circ = 0$). This temperature is referred to as the ceiling temperature T_c . The rate of polymerization at T_c equals the rate of depolymerization, that is, the net rate of polymerization is zero. Although a few polymerizations are endothermic ($\Delta H_p > 0$), they are also endotropic ($\Delta S_p > 0$). When these thermodynamic parameters operate, then an opposing phenomenon, the floor temperature T_f , is observed, below which no polymerization occurs. Finally, it also follows from Equation (2) that if $\Delta H_p > 0$ and $\Delta S_p < 0$, then polymerization of the monomer will not occur at any temperature.

Many condensation polymerizations involve equilibrium reactions. In such reactions the polymerization is said to be a

closed system if none of the products from the forward reaction are removed. Let us consider^[10] an acid-catalyzed polyesterification [Eq. (3)] in which the initial concentration of both the hydroxy and carboxy groups are $[M]_0$. The



concentration of both ester groups and water at equilibrium is given by $p[M]_0$, where p is the extent of the reaction at equilibrium. It follows that the concentrations of hydroxy and carboxy groups at equilibrium are each $([M]_0 - p[M]_0)$. The equilibrium constant K is then defined by Equation (4). This equation can be rearranged to give Equation (5), which gives the extent of conversion as a function of K . Equation (6) introduces an expression which states that the degree of polymerization is a function of K .

$$K = \frac{[\text{COO}][\text{H}_2\text{O}]}{[\text{COOH}][\text{OH}]} = \frac{(p[M]_0)^2}{([M]_0 - p[M]_0)^2} = \frac{p^2}{(1-p)^2} \quad (4)$$

$$p = K^{1/2} / (1 + K^{1/2}) \quad (5)$$

$$\bar{X}_n = 1 + K^{1/2} \quad (6)$$

Table 1 lists calculated values for different degrees of polymerization and the extent of reaction corresponding to various values of equilibrium constant K . The equilibrium constant for ester formation is around 1–10, while that for

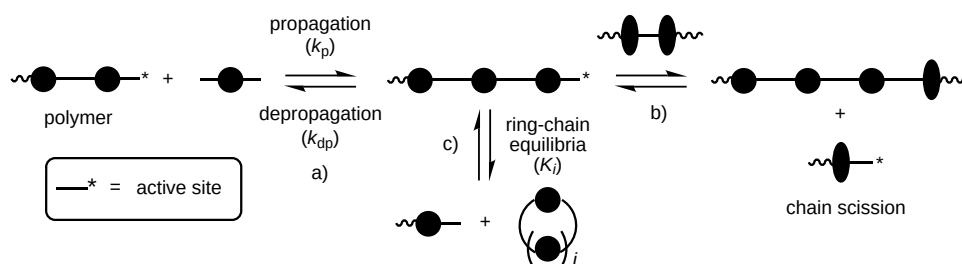
Table 1. The effect of the equilibrium constant on the degree of polymerization and extent of reaction in a closed system.

$\bar{X}_n$	p	K
2	0.500	1
20	0.950	361
50	0.980	2401
200	0.995	39601

amide formation is in the range of 10^2 – 10^3 . The data in Table 1 demonstrate that high molecular weight polymers cannot be obtained in closed systems, even in the case of polyamidation when the equilibrium constant is high. The outcome is that, in order to obtain high molecular weight polymers the system has to be driven, something that can be done in an open system where at least one of the products of the forward reaction is removed. It is usually more convenient to remove the by-product through a combination of physical (for example, temperature, reduced pressure, or purging with an inert gas) and/or chemical (for example, addition of base if

the by-product is an acid) methods, rather than attempting to remove the polymer. Just how the concentration of the water, or another condensation product, affects the degree of polymerization (number of repeat units) is expressed in Equation (7).

$$[\text{H}_2\text{O}] = \frac{K[M]_0}{\bar{X}_n(\bar{X}_n - 1)} \quad (7)$$



Scheme 2. Three different types of reversible processes that can occur during a dynamic polymerization: a) propagation/depropagation, b) chain scission, and c) ring-chain equilibria.

The concentration of water is essentially dependent upon the square of the degree of polymerization, which suggests that low concentrations of water are required to produce high molecular weight polymers. The extent to which the reaction must be driven—that is, the amount of condensation product that has to be removed—depends on the value of K for the reaction, as well as on the initial concentrations of the reactants. Table 2 shows the effect of small amounts of water on the degree of polymerization, when a condensation polymerization is carried out at $[M]_0 = 5\text{ M}$ for selected values

Table 2. The effect of water concentration on the degree of polymerization in an open, driven system.

K	$\bar{X}_n$	$[H_2O] [M]$
1	20	1.32×10^{-2}
	50	2.04×10^{-3}
	100	5.05×10^{-4}
	500	2.01×10^{-5}
361	50	0.725
	100	0.183
	200	4.54×10^{-2}
	500	7.25×10^{-3}

of K . Inspection of Table 2 reveals that it is easier, from an equilibrium point of view, to synthesize polyamides ($K = 10^2 - 10^3$) than polyesters ($K = 1 - 10$). From the same Table, it can be appreciated that the desired degree of polymerization can be obtained by controlling the amounts of condensation products (for example, water) remaining in the reaction vessel. Of course, systematically removing water results in the propagation step becoming less and less reversible. However, there are a variety of other equilibria, such as chain scission (Scheme 2b) or ring–chain interconversion (Scheme 2c), that may also be operating. Perhaps the most important of these reversible processes is the one involving ring–chain equilibria.^[22]

In 1950, Jacobson and Stockmayer^[23] published a theoretical account of this process based on the set of equilibria shown in Equation (8).



The equilibrium cyclization constant K_i is given by Equation (9)—always assuming that there is an adequate distribution of the chain lengths.

$$K_i = [M_i]/p^i \approx [M_i] \quad (9)$$

The extent of reaction p for most ring–chain equilibria is close to unity and so the values of K_i approximate to the molar concentration of the rings. When ring–chain equilibria are present, the equilibrium monomer concentration $[M]_e$ becomes a less important parameter since the formation of small- and medium-sized rings will also occur at equilibrium. To address this issue, Reif and Höcker^[24] have proposed the concept of the critical monomer concentration $[M]_c$, which is defined as the total amount of monomer present per unit volume that forms cyclic products according to the ring–chain equilibrium. If the mechanism of the reaction prohibits

cycle formation, for example, radical-chain polymerization, then $[M]_c$ is equal to $[M]_e$.

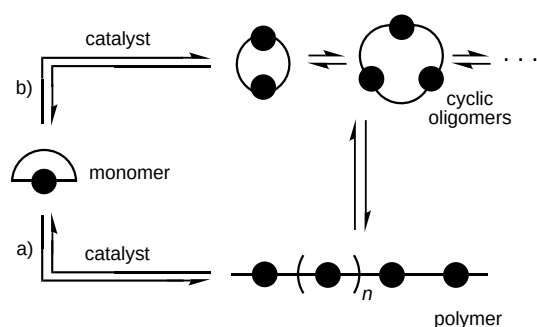
The Jacobson–Stockmayer (J-S) theory depends on four basic assumptions:

- 1) All rings are strainless and there is no heat of cyclization.
- 2) The end-to-end distances of linear chains obey Gaussian statistics.
- 3) The probability of ring formation is governed by the fraction of all the configurations in which the ends coincide.
- 4) The reactivity of each terminal functional group is independent of chain length.

On the basis of these considerations it was found that the equilibrium cyclization constant K_i decreases with increasing ring size as far as $i^{-5/2}$. Deviations of this theory from experimental data, particularly for “medium” and “small” rings, have been attributed to the failure of Gaussian statistics to predict accurately the properties of the chains to form rings. This research has led to a number of refinements of the original J-S theory—refinements which employ direct computational methods instead of relying upon the assumption that Gaussian statistics provide an accurate model. One can either use a rotational isomeric state model,^[22c,d] which models the conformational characteristics of a flexible polymer and their dependence on chemical configuration, and/or a modification of the J-S theory developed by Flory et al.^[25] which takes into account the directional requirements of the chain termini involved in the intramolecular cyclization. These modifications resulted in good correlations between theory and experiment for rings above about 25 backbone atoms. However, J-S theory and its refinements concentrate mainly on the entropic cost of forming rings, a situation which results in theory still over-estimating the proportions of smaller rings observed at equilibrium. Recently, further refinements to the theory have been made. They now take into account an enthalpic factor, that is, the ring strain of the smaller rings, which is calculated^[26] using molecular mechanics. The consideration of both enthalpic and entropic contributions allows for better predictions to be made of the critical monomer concentration $[M]_c$ and the equilibrium ring–chain distribution.

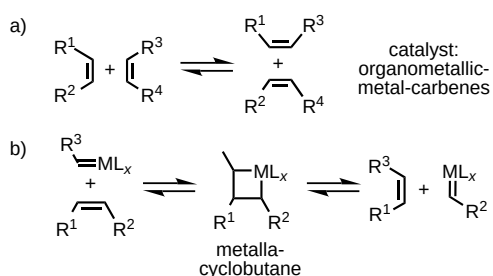
Equilibrium polymerizations, like living polymerizations, *ideally* do not have a termination step. However, depending upon the nature of the catalyst and the reaction conditions, most do have a termination step and this characteristic can result in polymerizations not reaching true equilibrium. In an ideal living polymerization^[27] all the polymer molecules start growing at the same time and the concentration of the active species stays constant, that is, there is no termination step. These characteristics result in an ability to control molecular weights and obtain narrow molecular weight distributions, as well as to prepare block co-polymers. However, most equilibrium polymerizations, such as certain ring-opening polymerizations, do not offer such capabilities, mainly because, in addition to the potential for depropagation, there is also the presence of a significant amount of “backbiting”^[28] and other mixing reactions, such as chain scission, caused by the reversible nature of the chemistry summarized in Scheme 2. If the reaction is allowed to reach equilibrium,

these “mixing” reactions effectively redistribute the monomer repeat units, which broadens the molecular weight distribution toward that of a broader Flory–Schultz “most probable” distribution, namely away from the observed narrow Poisson distribution of living systems, as well as creating more random distributions in the co-polymers. In thermodynamic chemistry we are concerned with the reactive stabilities of the final products and not how we get there. Even so, in ring-opening and some other step-growth polymerizations, there are two extreme pathways by which the final product polymer–cycle distribution can be achieved. The choice of pathway depends upon a number of factors, including monomer structure and concentration, catalytic activity, and temperature. At one possible extreme, the reaction could result in the formation of the polymer first before it then equilibrates with time to a mixture of polymer and cyclic oligomers (Scheme 3a). This mechanism pertains if the rate of polymerization is greater than the rate of backbiting. The other extreme case involves the initial formation of cyclic oligomers which then slowly converts (Scheme 3b) into an equilibrium mixture of the polymer and cyclic oligomers. Examples of these two different extreme models of behavior have been observed in ring-opening metathesis polymerizations (ROMP).



Scheme 3. Schematic representation of a ring-opening metathesis polymerization (ROMP) showing two different routes to the thermodynamic distribution of products: a) initial formation of high molecular weight polymer and b) initial formation of cyclic oligomers.

The olefin metathesis^[29] reaction (Scheme 4a) comes down to an apparent interchange of carbon atoms between two double bonds, which suggests that this process has the potential to be a reversible dynamic one. A range of organometallic reagents is known to catalyze the exchange reaction. The active catalytic species in most metathesis reactions are



Scheme 4. a) The olefin metathesis reaction and b) the mechanism involving a metallacyclobutane.

assumed to be metal carbenes and the reactions are believed to proceed via a metallacyclobutane intermediate (Scheme 4b). The rate of the olefin metathesis reaction is very sensitive to steric hindrance, a feature which means that the true thermodynamic products are only obtained with very reactive catalysts and/or nonsterically hindered olefins. In general, if the formation of the polymer occurs first, then the rate of polymerization is greater than the rate of backbiting. This situation can be achieved by using a) strained monomers, for example, 3-, 4-, or 8–10-membered ring compounds where there is a strong thermodynamic driving force to open up the rings, b) a mild catalyst, which is strong enough to ring-open the monomer, yet weak enough to not react with the more hindered double bonds in the polymer, and/or c) concentrations of the initial monomer which are high.

The polymerization of cyclooctene (**1**), by employing $\text{WCl}_6/\text{iBu}_2\text{AlCl}$ in benzene, follows this “polymer-first” pathway.^[30] During the polymerization (Figure 2), there is an initial sharp increase in the viscosity of the mixture and then, in the course of time, it decreases slowly. This behavior is explained by the initial formation of high molecular weight polymer, followed thereafter by the formation of a mixture of cyclic species and shorter polymers, which results in the observed decrease in the viscosity. In addition, the molecular weight distribution is observed to increase with time because of the mixing chain-transfer reactions.

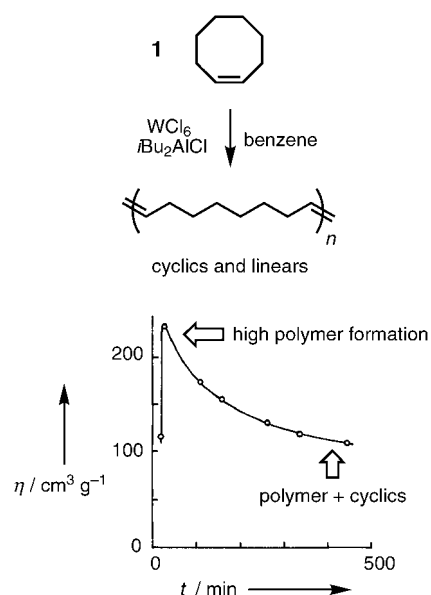


Figure 2. ROMP of cyclooctene (**1**) catalyzed by $\text{WCl}_6/\text{iBu}_2\text{AlCl}$ (1:5) in benzene at 25 °C together with a plot of intrinsic viscosity against reaction time. The graph shows the decrease in viscosity as the system comes to an equilibrium mixture of polymer and oligomers.

If, however, the rate of backbiting is greater than the rate of propagation, then oligomers will be formed initially, only to be followed by a conversion to the equilibrium mixture of cyclic species and polymers. This situation results when a) unstrained less reactive monomers (with, for example, a five-membered ring) in which there is no strong thermody-

namic driving force to open up the rings are used, b) a reactive catalyst, strong enough to undergo metathesis with the more hindered double bonds in the polymer is employed, and c) a low initial monomer concentration is used (although it still needs to be higher than the equilibrium (critical) monomer concentration). An example of a metathesis polymerization which appears to follow this route is the reaction of the *endo*-dicyclopentadiene **2** with $\text{ReCl}_5/\text{Me}_4\text{Sn}$ in CCl_4 .^[31] The amount of high molecular weight polymer and low molecular weight oligomers can be calculated from gel permeation chromatography (GPC) measurements. It was found that there is an initial sharp increase (Figure 3) in the amount of oligomers formed and then their formation decreases during the course of the reaction. Concurrently, after a small lag time, there is a steady increase in the amount of polymer formed, which suggests that it emanates from the oligomers and not from the monomers.

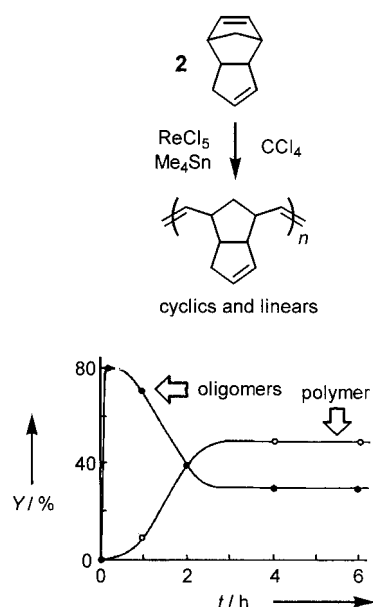
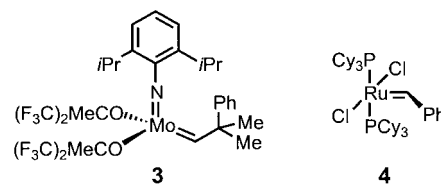


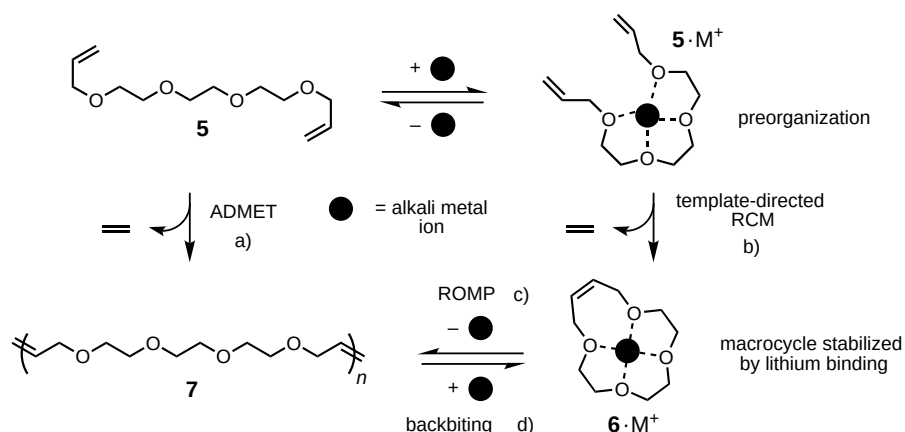
Figure 3. Variation in the yield *Y* of oligomers and polymers with time in the ROMP of **2** catalyzed by $\text{ReCl}_5:\text{Me}_4\text{Sn}$ (1:1) in CCl_4 at 50°C ; $[\text{M}]_0 = 3\text{ M}$.

In the two previous examples of olefin metathesis very reactive catalysts were employed, thereby restricting the functionality that could be present in the monomer. Recently, however, there have been major developments^[32] in the design and synthesis of well-defined organometallic reagents which catalyze olefin metathesis in the presence of a wide range of functional groups. The molybdenum alkoxyimido alkylidene **3**, developed by Schrock et al.,^[32] exhibits high reactivity toward a broad range of sterically and electronically different substrates. However, this catalyst suffers from extreme sensitivity to air and moisture and it cannot tolerate



the presence of particular functional groups. On the other hand, the benzylidene ruthenium complex **4**, developed by Grubbs and co-workers^[33] is not nearly as active, yet it does demonstrate good functional group tolerance.

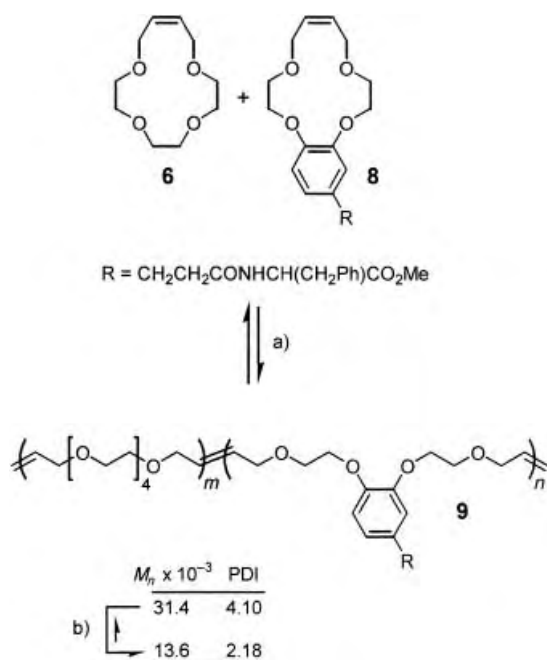
By utilizing this ruthenium catalyst, Grubbs and co-workers^[34] have examined the metathesis reaction of oligoethers, such as **5**, which contain allylic ether functionalities as their end groups. They demonstrate (Scheme 5) how reaction conditions can be used^[35] to alter product distributions in olefin metathesis reactions. The diallyl ether can be polymerized using an acyclic diene metathesis (ADMET) reaction to yield the low molecular weight ($M_n = 11\,200$) polymer **7**. The conditions for this reaction can be chosen to maximize the formation of the polymer (neat, under reduced pressure) and remove the volatile condensation product, ethylene. When the reaction is carried out in solution under dilute conditions (0.02 M), the major reaction is a ring-closing metathesis (RCM) which leads to macrocycle **6** (*cis:trans*, 38:62) in a 39% yield. If the reaction is carried out in the presence of lithium ions, the yield of the metal-bound macrocycle **6**· Li^+ can be increased to 95% (*cis:trans*, 100:0). There are two possible explanations for the observation of a template effect. They are: binding of a lithium ion to a linear polyether preorganizes the molecule for RCM—a kinetic templating effect—and/or binding of a metal ion stabilizes the macrocycle, thus lowering its energy and hence displacing the equilibrium toward the RCM product—a thermodynamic templating effect—(See Section 3.2). The resulting macrocycle **6**, after removal of the metal and purification, can then be subjected to ring-opening metathesis polymerizations (ROMP) in solution (1.2 M). Addition of the catalyst leads to the production of the polymer **7** ($M_n = 65\,900$). If the



Scheme 5. Template-directed metathesis reaction between **5**, **6**, and **7**. Reaction conditions: a) Grubbs' catalyst **4** (5 mol %), no template, 15 mTorr, 50°C ; b) **4** (5 mol %), metal template (5 equiv), $\text{CH}_2\text{Cl}_2:\text{THF}$, $[\text{M}]_0 = 0.02\text{ M}$, 45°C , 1 h; c) **4** (1 mol %), CH_2Cl_2 , $[\text{M}]_0 = 1.2\text{ M}$, RT; d) **4** (5 mol %), LiClO_4 (5 equiv), $\text{CH}_2\text{Cl}_2:\text{THF}$, $[\text{M}]_0 = 0.02\text{ M}$, 45°C , 75 min.

conditions are altered to favor macrocycle formation (that is, made more dilute (0.02 M), a higher temperature is used (50 °C) and/or in the presence of a template (Li^+ ions)), then **7** can be converted into macrocycle **6** in >95 % yield.

More recently, the same research group^[36] examined the copolymerization of macrocycle **6** with macrocycle **8** (Scheme 6). The co-polymer **9** was obtained ($M_n = 31\,400$, polydispersity index (PDI) = 4.10) upon reaction of the



Scheme 6. Copolymerization of **6** with **8** (25 mol % in feed) using Grubbs' catalyst **4**: a) **4**, $[\text{M}]:[\text{cat.}] = 100:1$, $[\text{M}] = 1.2 \text{ M}$, CH_2Cl_2 , 25 °C, 5 h; b) **4**, $[\text{repeat unit}]:[\text{cat.}] = 25:1$, $[\text{repeat unit}] = 2.4 \text{ M}$, CH_2Cl_2 , 25 °C, 1 week.

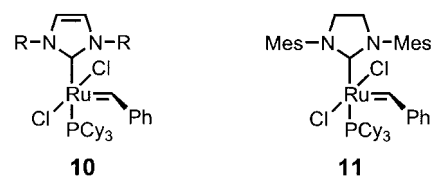
catalyst ($[\text{M}]:[\text{cat.}] = 100:1$) for five hours with the monomer feed (containing 25 % of **8**). The large polydispersity and presence of a high molecular weight shoulder on the GPC trace (Figure 4) indicate that the polymerization had not reached equilibrium, which suggests that the catalyst may have been deactivated. The loss of catalytic activity can be attributed to a small amount of isomerization of the allyl ether to vinyl ethers which are known to react with the ruthenium catalyst to form the metathesis-inactive $[\text{RuCl}_2(=\text{CHOR})(\text{PCy}_3)_2]$ (Cy = cyclohexyl) complex. The co-polymer, however, could be converted (Figure 4b) into the narrower molecular weight dispersed thermodynamic product ($M_n = 13\,600$, PDI = 2.18) by addition of a higher loading of fresh catalyst ($[\text{repeat unit}]:[\text{cat.}] = 25:1$) during a reaction time of one week. These conditions permit equilibration to take place through mixing processes such as backbiting. The same product distribution can be obtained directly (Figure 4c) from the macrocyclic monomer by using the same loading of catalyst and reaction time.

The example just discussed illustrates some of the drawbacks of using the ruthenium catalyst **4** in the arena of dynamic chemistry. The catalyst is not as active as some of the less functional group tolerant metal complexes and so only

reacts with highly reactive or unhindered olefins. This situation can result in a kinetically driven process unless long reaction times (days) are used (assuming the catalyst remains active) and/or the resulting products contain sterically accessible double bonds.

Recent developments in tuning the catalytic activity of the ruthenium metal complexes have resulted in a series of catalysts which display enhanced catalytic activities. Replacement of tricyclohexylphosphane ligands with the more Lewis basic imidazol-2-ylidene-derived ligands has resulted^[37] in catalysts such as **10** and **11** (Mes = mesityl = 2,4,6-trimethylphenyl) which, not only sustain increased reaction rates, but are also involved in the metathesis of olefins too sterically hindered to react with

4. Such “second generation” catalysts have been shown to be active enough to demonstrate the reversible nature of olefin metathesis reaction.^[38] The on-going development^[39] of such catalysts, which still display^[40] excellent functional group tolerance, will allow synthetic access to thermodynamically controlled functional materials by the olefin metathesis reaction.



The chief thermodynamic driving force in ring-opening polymerizations (ROP)—at least in the case of the smaller monomers—is the release of ring strain. In three- and four-membered rings, this driving force is caused by distortions in the bond angles and the stretching of the bonds, while in rings with eight to ten atoms, the impetus arises from the relief of unfavorable transannular interactions upon polymerization. Five- and seven-membered rings are more delicately balanced on account of the lack of strain observed in these rings. As such, they will either be very sensitive to polymerization conditions or they will not polymerize at all. By the time very large macrocycles are reached, the rings will become unstrained and the enthalpic term will be almost negligible since the same types of bond are being made and broken. However, polymerization occurs in the case of these monomers as a consequence of the increase in entropy in the polymer relative to that in the monomer—the entropic limits conferred upon a

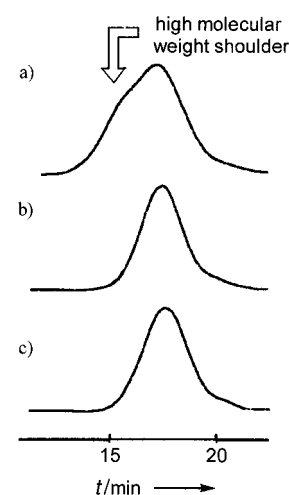


Figure 4. GPC traces for polymer **9a–c**: a) monomers (25 mol % of **8** in feedstock) polymerized for 5 h with **9a**; b) polymer **9a** subjected to $[\text{repeat unit}]:[\text{cat.}] = 25:1$ for 1 week to yield **9b**; c) monomers (25 mol % of **8** in feedstock) polymerized for 1 week with $[\text{M}]:[\text{cat.}] = 25:1$ to **9c**.

macrocycle can outweigh the entropic cost of bringing two molecules together. Polymerizations of such monomers are then said to be entropically driven and, in general, the larger the cyclic monomer, the more negative is ΔG° . An example of such an entropically driven polymerization is the macrocyclic ROP of carbonates shown in Scheme 7.

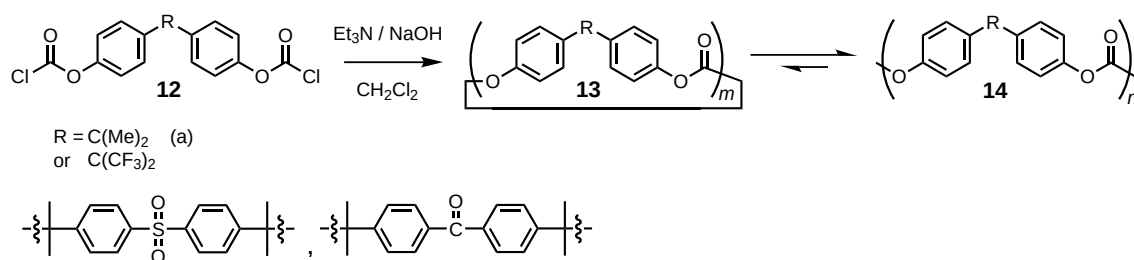
Brunelle and co-workers^[41] have developed a high-yielding synthesis of a variety of macrocyclic carbonates **13** by using a pseudo high dilution technique. This kinetically controlled procedure involves treating the monomeric bischloroformate **12** with an aqueous NaOH solution (in the presence of an amine catalyst) in a reaction^[42] which results in both hydrolysis and condensation to give the macrocyclic products **13** ($m = 2-20$) in high yields, typically 85%. Polymerization of these macrocycles can be induced^[43] using a variety of catalysts (basic or Lewis acidic) and conditions, for example, DMSO/ CH_2Cl_2 at ambient temperature or as a melt at 200–300 °C. The polymerization of the bisphenol A (BPA) macrocyclic derivatives **13a** ($R = \text{C}(\text{Me})_2$), for example, with $[\text{Ti}(\text{O}-i\text{Pr})_2(\text{acac})_2]$ (acac = acetylacetonate), results in the formation of commercially important BPA polycarbonate (**14a**; $M_w = 248\,000$, PDI = 2.5).

The equilibrating nature of the reactions results in the polymerizations of macrocyclic carbonates displaying some of the features of living polymerizations. Initiation by a nucleophile (for example, PhO^-) opens up the ring to afford a linear oligomer with a reactive chain end (Scheme 8). By controlling the ratio of monomer to catalyst, the number of chain ends formed can be altered and so the molecular weight

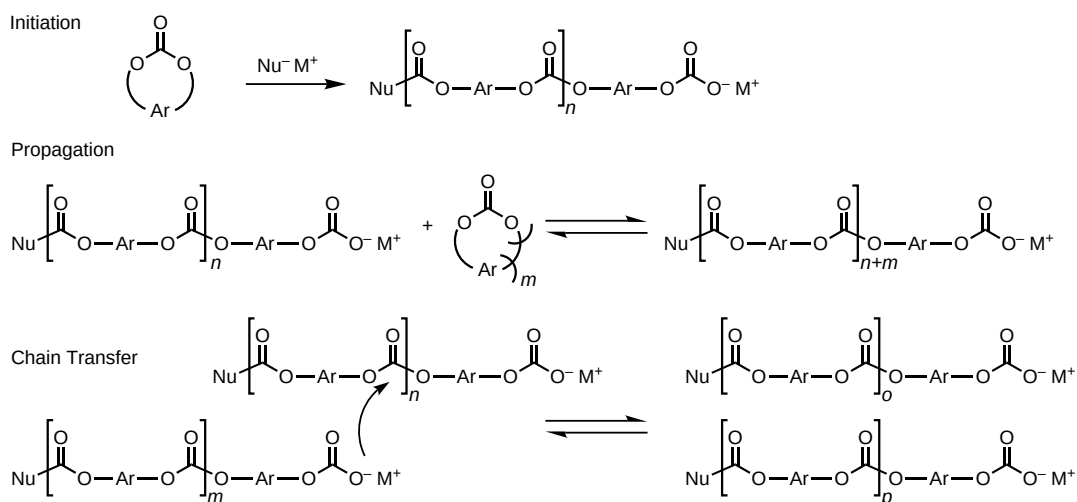
of the polymer can be tuned.^[44] Chain transfer agents, such as phenols or diarylcarbonates, can also be used^[45] to control the molecular weight of the polymer. On account of the size and conformation of the BPA-derived monomer units, the ring-chain equilibria favor the formation of the polymer chains and only a small percentage (0.25%) of the cyclic species is present at equilibrium. However, chain–chain (chain scission) equilibration, which occurs concurrently with the propagation, results in the polydispersities of the polymers approaching 2.0, that is, the most probable distribution. The structure of the monomer unit has a large effect upon both the kinetic cyclization and the thermodynamic polymerization. The spirobi(indane) bisphenol **15** has a rigid bent structure and, as such, the syntheses of the macrocyclic monomers (Scheme 9) are more expedient and lead to 95% of the products being macrocycles, mostly the cyclic dimer **16** ($n = 1$). However, although the macrocyclic monomers can be polymerized, they are present in the equilibrated mixture at an increased percentage (9%) compared with the BPA derivatives.

The macrocyclic ring-opening polymerization offers a number of attractive features:^[46]

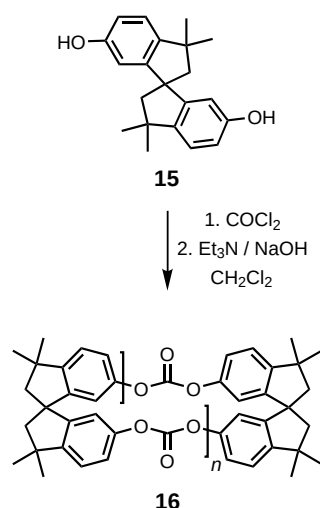
- 1) In contrast to conventional step-growth polymerizations, there are no condensation products generated during these reactions, which thus allows the formation of void-free polymers in situ.
- 2) The viscosities of the macrocyclic monomers are generally significantly lower than those of the high molecular weight polymers, thus facilitating reactive processing.



Scheme 7. Kinetic formation of the macrocyclic carbonates **13** ($m = 2-20$) and their subsequent thermodynamic polymerization to yield the polycarbonates **14**.



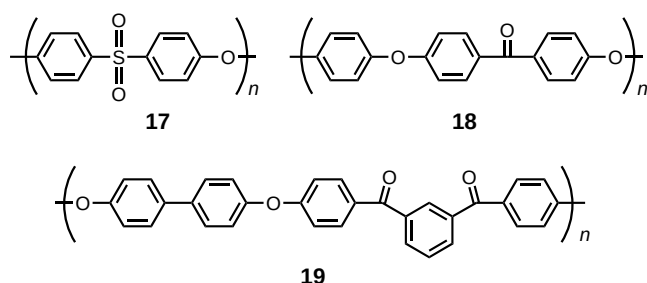
Scheme 8. Proposed mechanism for the dynamic polymerization of the macrocyclic carbonates **13**.



Scheme 9. Kinetic cyclization of the spirobi(indane) bisphenol **15** which results in a high yield (95%) of macrocyclic products **16**, probably on account of the rigid bent structure of the monomer.

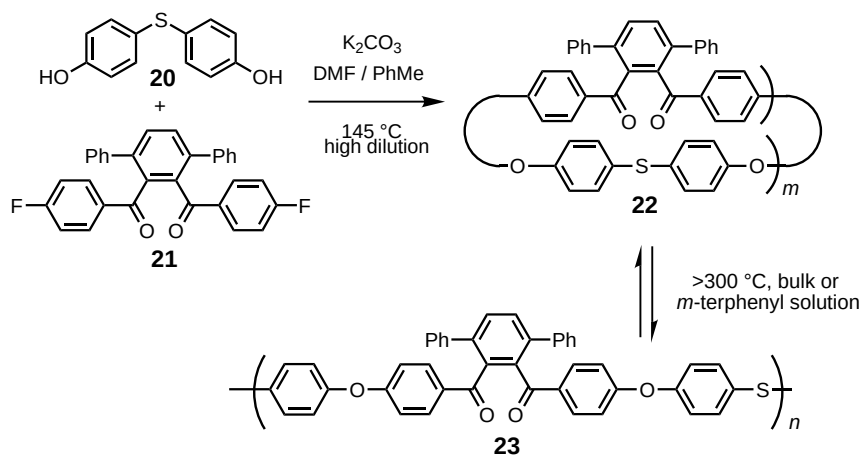
- 3) The mixture of cyclic monomers lowers their melting points, which allows melt processes during ROP to occur at lower temperatures.
- 4) The reactions, being entropically driven, are thermoneutral, and so, unlike small-ring ROP, there is no large build up of heat.

The polymerization of the BPA macrocyclic derivatives **13a** (Scheme 7) are only slightly exothermic (-1.2 kJ mol^{-1}); this situation is caused mainly by the release of ring strain in the cyclic dimer.^[47] Monomers with functionalities other than carbonates, for example, macrocyclic esters^[48] and diaryl ethers,^[49] have also been prepared and shown to undergo macrocyclic ring-opening polymerizations. The use of the diaryl ether functionality as the dynamic bond has been the key to the synthesis of a series of high-performance aromatic polymers,^[50] for example, poly(ether sulfone)^[51] **17**, poly(ether ether ketone)^[52] **18**, and the poly(ether ketone) “PK99”^[53] **19**, from macrocyclic monomers.



An interesting diaryl ether (Scheme 10) was reported in 1996 by Hay and co-workers.^[54] The macrocycle was prepared by the formation of the diaryl ether bond from di(4-

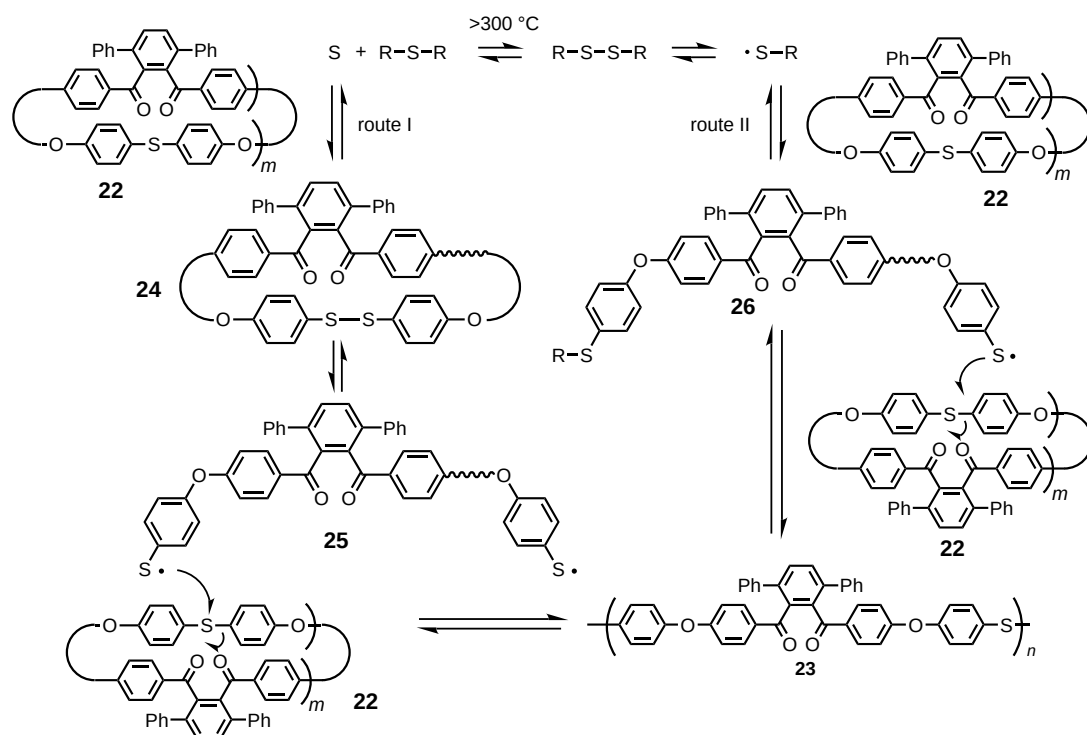
hydroxybenzyl)sulfide (**20**) and 1,2-bis(4-fluorobenzoyl)-3,6-diphenylbenzene (**21**) under high dilution. However, the resulting macrocycles **22** can be polymerized at high temperatures (for example, in *m*-terphenyl at 380°C) without breaking the diaryl ether bond. Instead, thermally induced homolytic cleavage of the aryl carbon–sulfur bond yields^[55] an aryl radical and a sulfanyl radical, which, in turn propagates the polymerization, through a radical aromatic substitution, to afford the polymer **23** ($M_n = 18300$) after 30 mins. The reaction can be catalyzed by the addition of either elemental sulfur or by a diaryl disulfide which leads to a second equilibration process, which consists of the interconversion of a diaryl disulfide with sulfur and diaryl sulfide. This exchange reaction opens up two possible routes for the polymerization (Scheme 11): either through the formation (route I) of the macrocyclic disulfide **24** or the attack (route II) of the macrocyclic monomer **22** by the aryl sulfanyl radical. In both cases, homolytic cleavage of the disulfide bonds yields the sulfanyl radicals (**25** and **26**) required for the



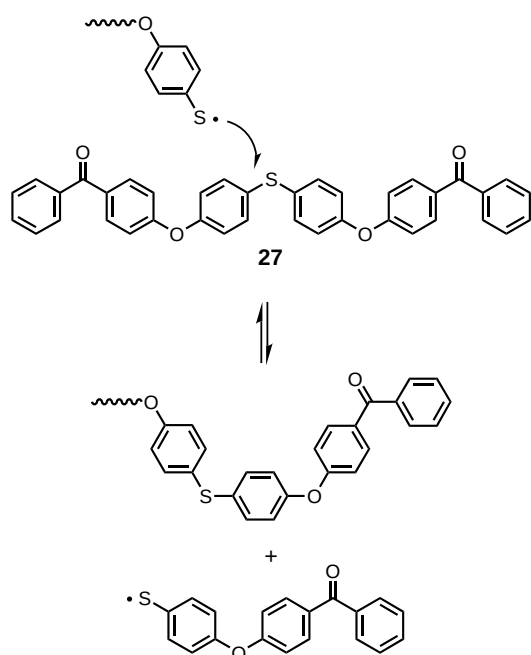
Scheme 10. Kinetic formation of macrocyclic monomers **22** from **20** and **21** and their subsequent high-temperature polymerization under thermodynamic control to give the polymer **23**.

polymerization. The reaction exhibits chain–chain, as well as ring–chain equilibria, a feature which leads to the control of the molecular weight of the polymer by the addition of the thioether **27** (Scheme 12). There are also reports^[56] of diaryl thioethers in which ring-opening polymerization is catalyzed by anionic phenolates.

The reverse of macrocyclic ROP is ring-closing or cyclo-depolymerization (CDP) which, on account of the reversible nature of the reactions, occurs when the equilibration process is carried out under conditions that favor the formation of cyclics, namely high dilution. CDP has been carried out on a series of aromatic diaryl ether polymers. At high temperatures, and in the presence of a strong but kinetically labile nucleophile, such as fluoride or phenolate ions, the transesterification can take place (Scheme 13). The reversible reaction is a nucleophilic aromatic substitution and, as such, is greatly facilitated by the presence of an electron-withdrawing group (usually SO_2 or $\text{C}=\text{O}$) in either the *ortho* or *para* positions relative to the nucleophilic site. Colquhoun and co-workers^[57] have described a number of these systems. The

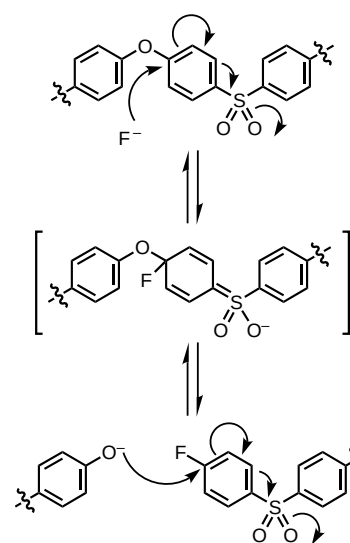


Scheme 11. Proposed mechanism of the thermodynamic polymerization of **22** to **23**. The interconversion of a diaryl sulfide with sulfur and a diaryl disulfide allows two possible mechanistic routes: formation (route I) of **24** and/or attack (route II) of **22** by the arylsulfanyl radical.



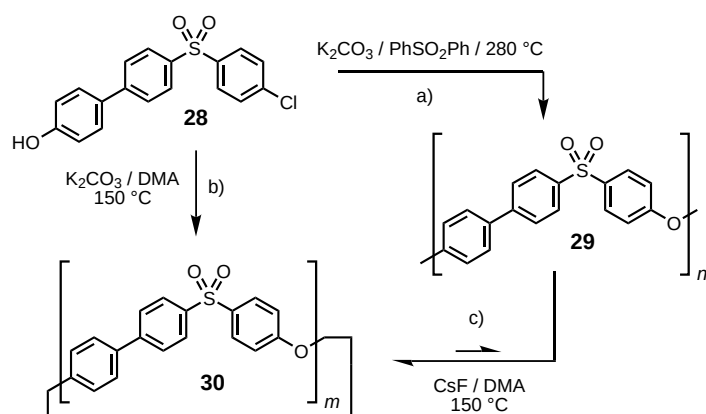
Scheme 12. The mechanism by which **27** acts as a chain-transfer agent, rationalizing how **27** can be used to regulate the molecular weight of polymer **23** during the high-temperature polymerization (Scheme 10) of **22**.

monomer **28** can be polymerized (Scheme 14) by standard step-growth polymerization to yield polymer **29**. When **29** ($M_n=8500$ and $M_w=29000$) is submitted to equilibrating conditions (CsF in dimethylacetamide at 150°C) at a monomer equivalent concentration of 0.03M , then CDP of the polymer is observed, which results in the formation of



Scheme 13. The fluoride-catalyzed transesterification of poly(ether sulfones).

macrocycles **30** ($m=3-9$). Figure 5 shows the GPC trace of the polymer ($t=0\text{ h}$) before the addition of the catalyst and indicates the presence of a small amount of macrocycles that were formed during the synthesis of the polymer. The concentration of the macrocycles increases with time ($t=5\text{ h}$) upon addition of the catalyst and reaches an equilibrium after 48 h. The resulting products were identical (by GPC and HPLC) to macrocycles formed by the cyclization of monomer **28** under similar reaction conditions (K_2CO_3 in DMF at 150°C under high dilution). The potential to depolymerize (CDP)



Scheme 14. a) Step-growth polymerization of **28** to yield **29**; b) kinetically controlled cyclization of **28**; and c) fluoride-catalyzed ring-closing depolymerization of **29**.

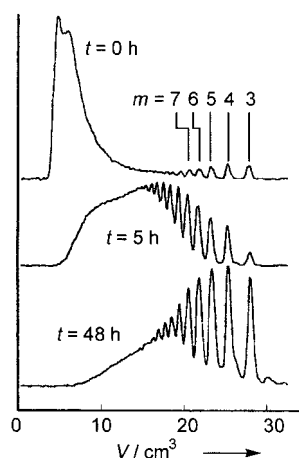


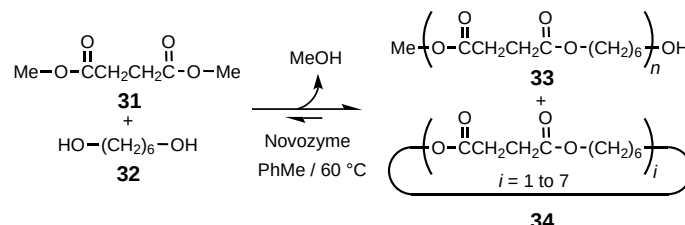
Figure 5. GPC profile of **29**, formed by the polymerization of monomer **28** before the addition of any catalyst ($t=0$ h). The GPC profiles of the fluoride-catalyzed ring-closing depolymerization of polymer **29**, after $t=5$ h and $t=48$ h indicate an increase in the amount of macrocycles **30** with time. (m = number of repeat units in the macrocycles.)

and repolymerize (ROP) these polymers opens up the possibility of recycling these high-performance aromatic polymers.

In general, CDP offers the possibility of recycling any polymer which contains a dynamic bond. The reversibility of the ester bond and the wide range of possible transesterification catalysts^[58] make polyesters attractive candidates for this kind of dynamic chemistry. The reversible nature of bond-forming and bond-breaking processes in polyesters has been known and investigated for a number of years.^[59] Recent studies carried out on the CDP of polyesters have focused^[60] on thermodynamic recycling of the naturally occurring poly(*(R)*-3-hydroxybutyrate), as well as on the use^[61] of polyesters as feedstocks for macrocycles and/or combinatorial libraries (see Section 4) and the use of enzymes as catalysts for both the polymerization and depolymerization of esters.^[62]

In a series of papers Brigodiot, Lalot, Maréchal, and co-workers^[63] have described their investigations on the enzyme-catalyzed ring-chain equilibrations of a number of polyesters. They have demonstrated^[64] that the polymerization between a number of diesters and diols with the Novozyme catalyst (a two-component enzymatic catalyst containing two lipases

immobilized on a macroporous acrylic resin) has all the characteristics of a dynamic process. For example, when dimethyl succinate (**31**) and 1,6-hexanediol (**32**) were heated (Scheme 15) in toluene at 60 °C and using a nitrogen flow to remove the methanol, then the formation of the polyester **33**, as well as the cyclic esters **34** (rings $i=1-7$ with M_n not



Scheme 15. Enzyme-catalyzed transesterification of **31** and **32**.

exceeding 3000), were observed. The team also carried out a series of experiments designed to test the reversibility of the enzyme-catalyzed polymerization. As expected, dilution of the reaction mixture led to an increase in the proportion of the rings formed and a decrease in the molecular weight of the polymer formed. Figure 6a and c show the GPC profiles of the reactions carried out at 0.05 and 0.4 M, respectively. The increase in concentration results in the formation of a larger proportion of higher cyclic oligomers as well as of polymer. Moreover, the cyclic mixture obtained from the reaction (0.05 M) was submitted once again to the equilibrating enzyme-catalyzed conditions at the highest concentration (0.4 M). The result was the establishment of essentially the same product distribution (Figure 6b) as had been observed in the reaction that was carried out initially at 0.4 M (Figure 6c). In the proposed propagation mechanism (Scheme 16), a hydroxy group in the active site of the lipase undergoes a transesterification with the ester-containing monomer unit to give an acylated enzyme intermediate. The second step involves a second transesterification between an alcohol and the acylated enzyme intermediate. Although there are a number of possible intermediates, it is only the ω -hydroxyacyl enzyme that can lead to the formation of rings. The distribution of the ring sizes for $i > 1$ was found to follow the theoretical Jacobson–

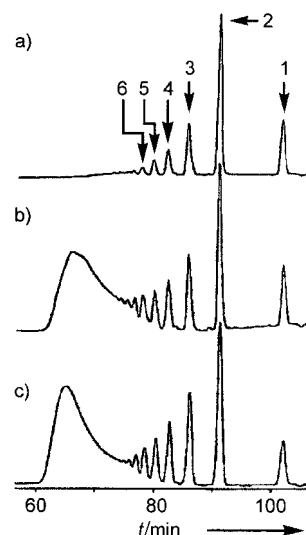
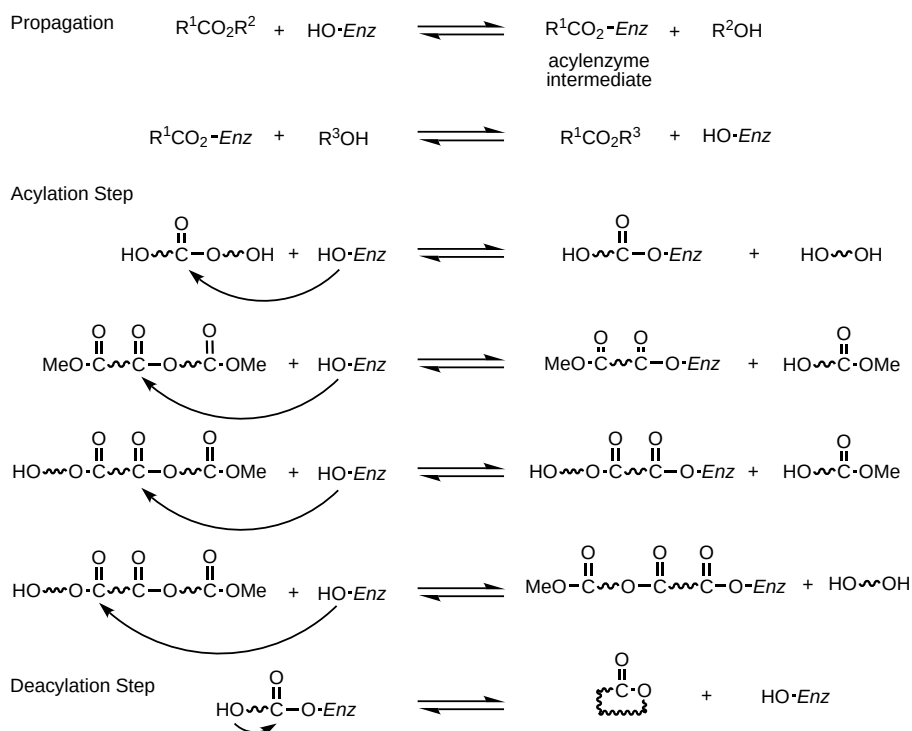
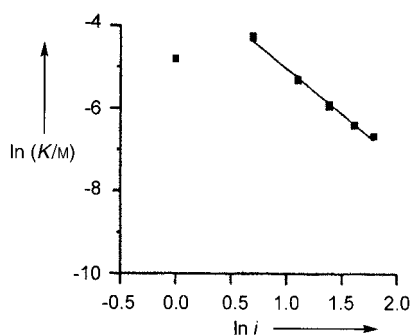


Figure 6. GPC profiles: a) the ring-chain mixture obtained from **31** and **32** (initial concentration of reactive functions $c_0 = 0.05 \text{ mol L}^{-1}$); b) the same sample dissolved in toluene (40 g L^{-1}) and heated at 60 °C for 1 day in the presence of the enzyme; c) the ring-chain mixture obtained directly from **31** and **32** ($c_0 = 0.4 \text{ mol L}^{-1}$). The unimolecular peaks were assigned to rings with $i=1-6$ (i = number of each monomer type in the rings).



Scheme 16. Proposed mechanism for an enzyme-catalyzed transesterification (Scheme 15).

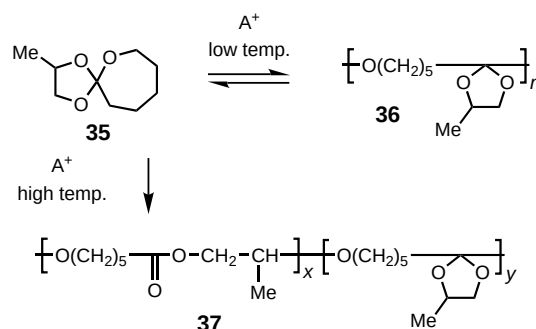
Stockmayer (J-S) relationship (Figure 7). There is, however, a discrepancy between the predicted amount of the smallest macrocycle ($i=1$) and the actual quantity formed. This discrepancy may arise, in part, from a small enthalpic contribution from ring strain which is not taken into account


 Figure 7. Experimental molar cyclization equilibrium constants K for compounds in a solution of **33** in toluene ($c_0 = 0.4\text{ M}$) at 60°C as a function of i .

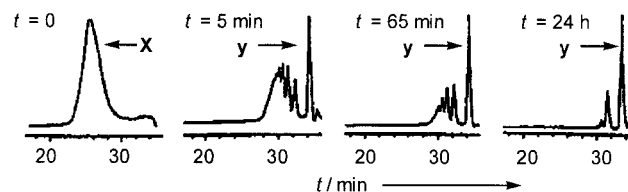
by J-S theory. However, this discrepancy in the cyclization equilibrium constant for the smallest ring is large when compared with the same reaction where $[\text{Ti}(\text{O}-i\text{Pr})_4]$ is the catalyst instead of the enzyme. K_1 values of approximately 25 and 9.7 mm^{-1} were calculated, respectively, for the $[\text{Ti}(\text{O}-i\text{Pr})_4]$ - and the enzyme-catalyzed reactions on the basis of the amount of macrocycle formed. While the two reactions were carried out under slightly different conditions, the authors suggest that the difference in these equilibrium constants may reside in the strain induced in the smaller ring as a result of the conformational changes which are required

to facilitate the binding of the enzyme to the macrocycle. If these conformational changes destabilize the ring, then the outcome would be the observed decrease in the proportion of the smallest ring present in the reaction mixture.

Endo et al.^[65] have demonstrated that thermodynamic control is observed in the polymerization of spiro-orthoesters such as **35**. This interesting ring-opening reaction can lead to different repeating units in the polymers, depending on the particular reaction conditions (Scheme 17). The more-strained seven-membered ring can react with cationic initiators such as SnCl_4 to yield the poly(orthoester) **36**. Although this single ring-opening polymerization occurs at temperatures below 0°C , a polymer **37** containing a mixture of poly(orthoester) and double ring opening poly(ether ester) repeating units is observed at higher temperatures.^[66] The ratio of poly(ether ester) to poly(orthoester) repeating units increases as the temperature of the reaction is raised. The cationic polymerization of **35** to **36**


 Scheme 17. Cationic ring-opening polymerization of **35** can yield either **36** (through a reversible, single seven-membered ring-opening process at low temperatures) or **37** (through an irreversible tandem ring-opening process with isomerization at higher temperatures).

($2\text{ M CH}_2\text{Cl}_2$ at -50°C , $M_n = 9770$, $M_w/M_n = 1.89$) has been shown^[65b] to display the characteristics of an equilibration process (Figure 8): 1) the addition of HCl to a dilute (58 mM) solution of the polymer results in the formation of monomer, 2) the molecular weight of the polymer decreases with


 Figure 8. Change in the GPC profile with time for the depolymerization of **36** (58 mM , x) with HCl ($2\text{ mol \%}$) at 25°C in CH_2Cl_2 showing an increasing yield of macrocycle **35** (y).

increasing temperature, 3) $[M]_e$ increases with rising temperature and, in accordance with Equation (2), shows a linear dependence of $\ln[M]_e$ with $1/T$ (Figure 9), which allows by extrapolation the deduction to be made that $\Delta H^\circ = -8.0 \text{ kJ mol}^{-1}$, $\Delta S^\circ = -30.7 \text{ J mol}^{-1} \text{ K}^{-1}$, and $T_c = 254 \text{ K}$, and 4) the molecular weight distribution is centered around the most probable (theoretical) distribution of 2.

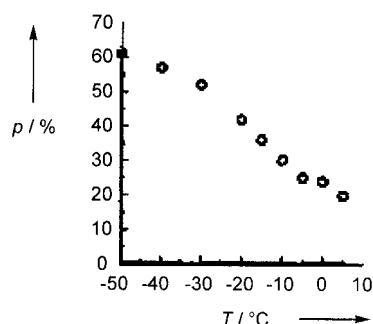
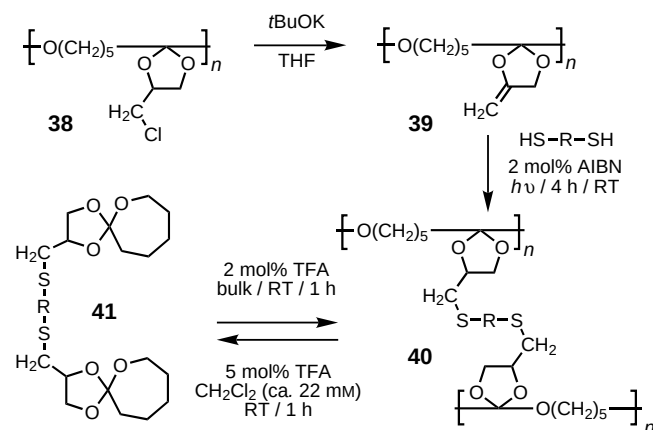


Figure 9. Dependence of the conversion p on temperature T for the polymerizations of **35** in CH_2Cl_2 (**35**, 2 M) with SnCl_4 (2 mol %) for 1 h.

Endo et al.^[67] went on to investigate the possibility of employing this reaction to synthesize reversible networks. The poly(orthoester) **39** ($M_n = 4900$, $M_w/M_n = 2.13$) possessing an exomethylene group,^[68] prepared by dehydrochlorination of poly(chloromethyl orthoester) **38** with $t\text{BuOK}$, was cross-linked^[69] by the radical addition of a dithiol (for example, 1,3-propanedithiol) across the double bond to afford the cross-linked network **40** in 67% yield (Scheme 18). This network

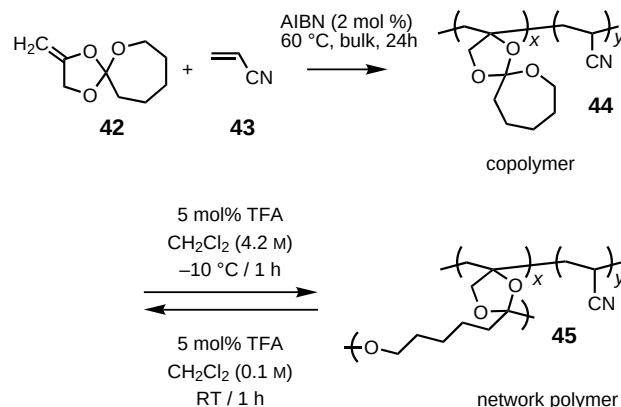


Scheme 18. Synthesis of **40** from the radical addition of dithiols to **39**. The resulting network undergoes interconversion with **41** in the presence of acid.

could then be depolymerized by suspending it in CH_2Cl_2 (20 mM) and treating it with TFA (5 mol %) to give the bifunctional monomer **41** in 60% yield. Monomer **41** could also be synthesized by radical addition of 1,3-propanedithiol to the exomethylene spiro-orthoester **42**. The monomer **41** undergoes polymerization with 2 mol % TFA in the bulk to afford the cross-linked polymer **40**. As in most equilibrium-controlled polymerizations, the temperature plays a critical role in determining the yield of the polymer **40**. Although the

polymer was isolated in 52% yield at 0°C , the equilibrium shifts at a higher temperature (30°C) to the side of the monomer **41** (19% yield of polymer). In this case, the polymer network could be recycled to a bifunctional monomer.^[70]

Endo et al.^[71] have investigated a polymer network that can be interconverted with a linear polymer (Scheme 19). Orthoester **42** was copolymerized with an equivalent of the acrylonitrile **43** in a reaction initiated by azobisisobutyronitrile (AIBN) in the bulk at 60°C . This led to the copolymer **44** ($M_n = 46000$, $M_w/M_n = 2.27$, $x:y = 44:56$) in 85% yield. The



Scheme 19. Radical copolymerization of **42** with **43** to yield polymer **44**. The network polymer **45** can be obtained by using acid catalysis at high concentration (4.2 M). In addition, **44** can be regenerated from **45** by treatment with TFA at low concentration (0.1 M).

cross-linking reaction was carried out in CH_2Cl_2 containing 5 mol % of TFA over a range of concentrations. At 0°C , significant cross-linking (>50% yield of cross-linked polymer) was only observed at >4 M. By contrast, treatment of the network polymer **45** at a lower concentration (0.1 M) at room temperature results in its reversion to the linear copolymer **44**. The de-cross-linking of the polymer network also increases with temperature. Above 30°C , an irreversible double ring-opening reaction to give the ester was also observed.

The reversible nature of imine bond formation^[72] makes it an attractive process for use in dynamic synthetic chemistry. There are three reversible reactions (Figure 10) in which imines may potentially participate. The first is simply the formation and hydrolysis of the imine bond. In this instance,

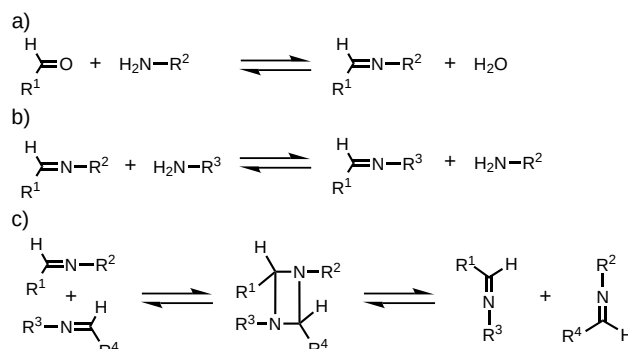
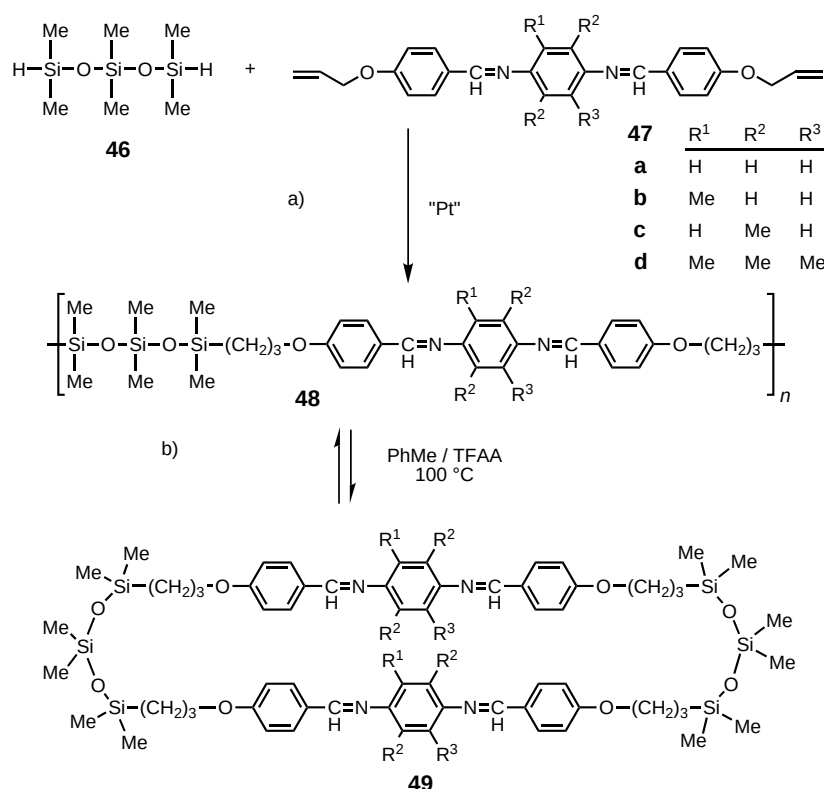


Figure 10. Three potentially reversible reactions of the imine bond: a) imine hydrolysis/formation, b) imine exchange, c) imine metathesis.

exchange occurs between either an aldehyde or ketone plus an amine and an imine, with water being the nucleophilic species that interconverts the functional groups. The second is the imine exchange reaction in which the nucleophile is simply another amine. The third is the imine metathesis reaction. Although a transamination mechanism was proposed for this reaction a number of years ago by Tóth and co-workers,^[73] it is only recently, with the development of specific organometallic catalysts (analogous to the olefin metathesis catalysts) which facilitate the exchange between two imines,^[74] that the imine metathesis reaction has received more attention.

The dynamic nature of the imine bond has been demonstrated in polymer systems with the existence of ring–chain equilibria such as those which have been observed in main-chain thermotropic aromatic polyazomethines that contain flexible siloxane spacers.^[75] The amount of macrocycle formed was shown to depend upon a number of factors, such as concentration, temperature, and solvent, as well as on the length of the flexible siloxane spacer; less macrocycle is formed when there are more than three Si–O functional groups. The synthesis of the polymer was achieved (Scheme 20) as a result of a polyhydrosilylation process by treating hexamethyltrisiloxane (**46**) with the diallyloxyazomethine compounds **47a–d** in the presence of a Pt catalyst to give a mixture of the polymers **48** with the macrocycles **49**. Figure 11 shows the GPC traces for the polymerizations and macrocyclizations of a series of compounds which differ in their degrees of methyl substitution on the central aromatic



Scheme 20. a) Polyhydrosilylation of **46** with **47a–d** in the presence of a Pt catalyst. b) Equilibration of the polymers at 100 °C with an acid catalyst results in more of the macrocycles **49**. Head-to-head isomers, as well as the head-to-tail isomers shown, are also possible in the case of **47b**.

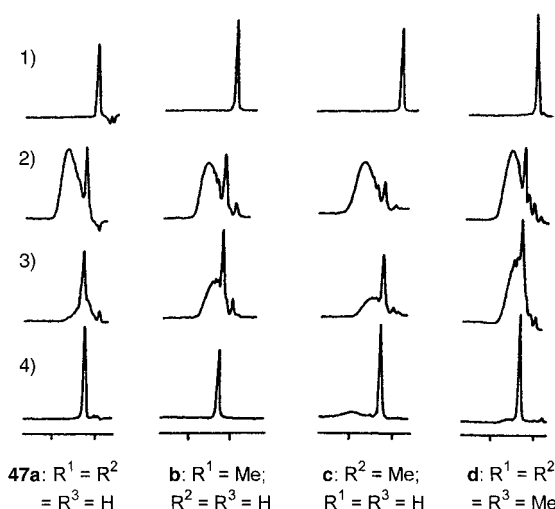


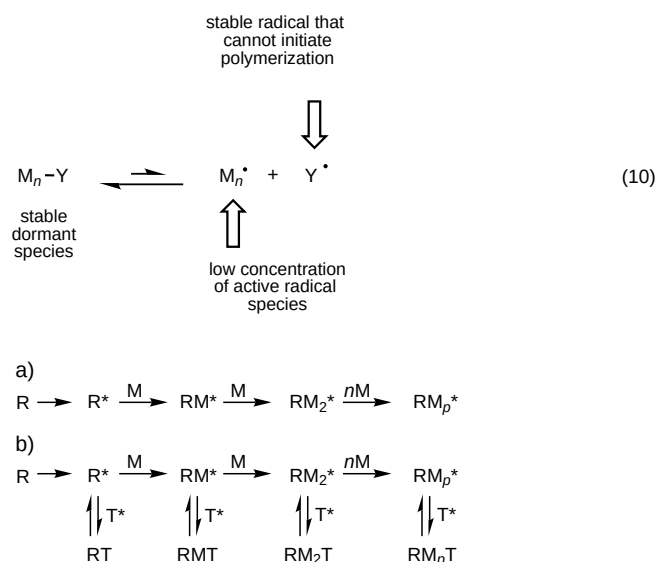
Figure 11. GPC traces of 1) diallyloxy starting materials (**47a–d**) before reaction, 2) linear polymer **48** after hydrosilylation, 3) reaction medium after equilibration in acid, and 4) the macrocycles obtained after the first precipitation.

ring.^[76] The reaction mixtures could be equilibrated by heating (100 °C) them in toluene in the presence of acid, a procedure which resulted in more of the macrocycles **49** being formed. The degree of substitution on the central aromatic ring affects the amounts and rates of macrocycle formation: the more highly substituted the rings, the slower are the exchange reactions and the lower are the yields of macrocycles. The macrocycles **49** were isolated by precipitation from the toluene reaction mixture at room temperature.

This procedure effectively “traps” the macrocycles, preventing them from re-equilibrating, through the ring–chain equilibria, with their respective polymers.

2.2. Reversible Initiation/Termination

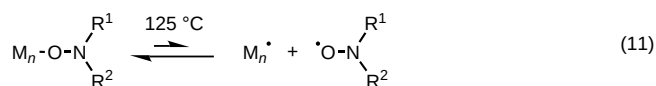
The concept of reversible initiation/termination has led to a revolution in both the cationic^[77] and free-radical^[78] polymerizations of olefins. The reversible chemistry allows control of the polymerization process such that it starts to behave like a living system. The equilibrium interconverts [Eq. (10)] the active propagating species with a covalent dormant species. If the equilibrium lies toward the side of the dormant species, then this situation limits the number of active species present in the system and so helps to control the outcome of the reaction by reducing the amount of irreversible termination and chain-transfer processes. The equilibration should be faster than the irreversible propagation step which results in the formation of the polymer under kinetic control. Indeed, these “controlled” polymerizations (Scheme 21) are not true living sys-



Scheme 21. a) Polymerization in a living system shows no termination or chain transfer. b) Polymerization in a controlled polymerization system uses reversible termination to control the number of active species and so reduces the significance of irreversible termination processes. R = radical initiator, M = monomer, T = “dynamic” terminating group.

tems^[79] since chain termination and transfer do occur, albeit at a much reduced rate. However, the reversible nature of the initiation/termination process can result in the polymerization displaying living behavior, namely, control of molecular weight and molecular weight distributions, as well as the production of block copolymers, are all possible.

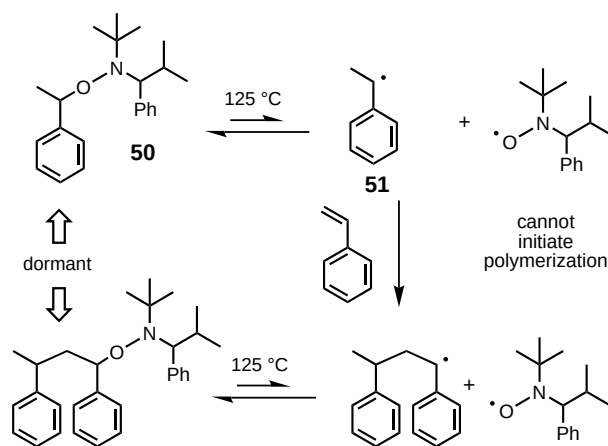
One example of this reversible initiation/termination process, which leads to a pseudo living system, utilizes the thermally induced homolytic cleavage of alkoxyamines to yield reversibly a nitroxide and a propagating free radical.^[78a] At 125 °C, a proportion of the C–O bonds in an alkoxyamine are cleaved homolytically in an initiation step [Eq. (11)],



which results in the formation of a nitroxide and a benzylic radical. In the specific example described in Scheme 22, it can be seen how these radicals can recombine to reform the alkoxyamine **50** or instead how the benzylic radical **51** can react with styrene in a propagation step. Thereafter, the nitroxide can react with the new benzylic radical, in a termination step, to form a “chain-increased” alkoxyamine. The process can then be repeated to form the polymer. The low concentration of propagating radicals reduces the likelihood that termination will occur by a combination process, a feature which allows the system to develop its “living” characteristics.

3. Equilibrium (Dynamic) Reactions

The self-assembly of discrete well-defined supramolecular architectures involves the spontaneous noncovalent aggrega-



Scheme 22. The controlled polymerization of styrene using **50** as the initiator.

tion of molecules under thermodynamic control.^[7] In recent years, a number of research groups worldwide have started to investigate the potential of dynamic covalent chemistry as a means to build precise molecular architectures. In common with supramolecular chemistry, dynamic covalent chemistry operates under thermodynamic control. It relies on the making and breaking of covalent bonds as an on-going process in a chemical reaction. Dynamic covalent chemistry can aid and abet the efficient synthesis of molecular compounds—often those that have proved difficult to synthesize by standard irreversible, kinetically controlled, covalent bond forming chemistry—provided the compounds have considerable relative thermodynamic stabilities.^[80] In this section, we will outline how certain molecular compounds have been prepared efficiently both with and without the involvement of templates.

3.1. Cyclic Compounds

In a monograph on “Stereochemistry of Carbohydrates” written^[81] by one of us (J. F. Stoddart) over 30 years ago, the following concluding statement was made at the end of the final chapter: “The fact that constitutional, configurational, and conformational isomerisms are often superimposed on each other would almost seem to confer on carbohydrates a unique status amongst organic compounds.” Indeed, these facile isomerisms, involving five- and six-membered rings for the most part, provided a gigantic and fertile playground for covalent dynamic chemistry to express itself in some quite remarkable ways, many of which must have been quite surprising and puzzling to researchers of a century or more ago and yet are readily amenable today to simple stereochemical analysis or, if not, intense computational investigation. The very fact that, in classical carbohydrate chemistry,^[82] some deceptively simple reactions (for example, methyl glycoside formation in methanol in the presence of an acid catalyst) of aldohexoses give at least a four-component equilibrium mixture of cyclic thermodynamic products (furanosides and pyranosides with both α and β configurations) while other reactions (for example, phenylosazone formation,

which was so important in the establishment of the configurations of the carbohydrates by Fischer) of the same aldohexoses give only one acyclic kinetic product (a water-insoluble phenylosazone) when they are treated in aqueous solution with phenylhydrazine is more than adequate demonstration of the dynamic nature of covalent bonds associated with the anomeric centers in free sugars.

Cyclic acetal formation under conditions of acid catalysis provides yet another example^[81] of a well-known reaction where covalent bonds are made and broken easily under thermodynamic control. A good example^[83] is provided by the acid-catalyzed reaction of glycerol with isobutyraldehyde. Since the activation energy is less for the formation of the five-membered (dioxolane) ring compounds (*cis* and *trans* isomers) than for the six-membered ring compounds, they are formed faster under kinetic control ($k_5 > k_6$; Figure 12).

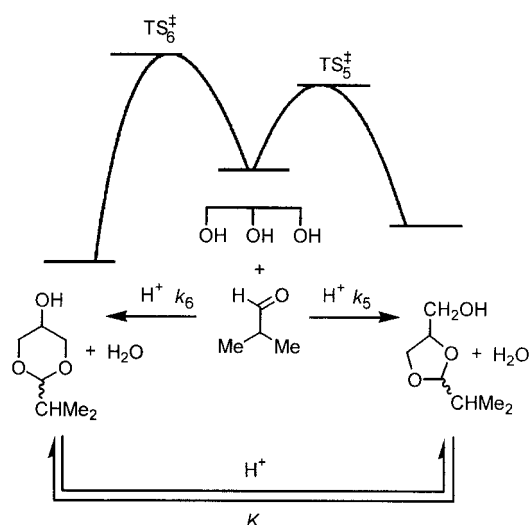
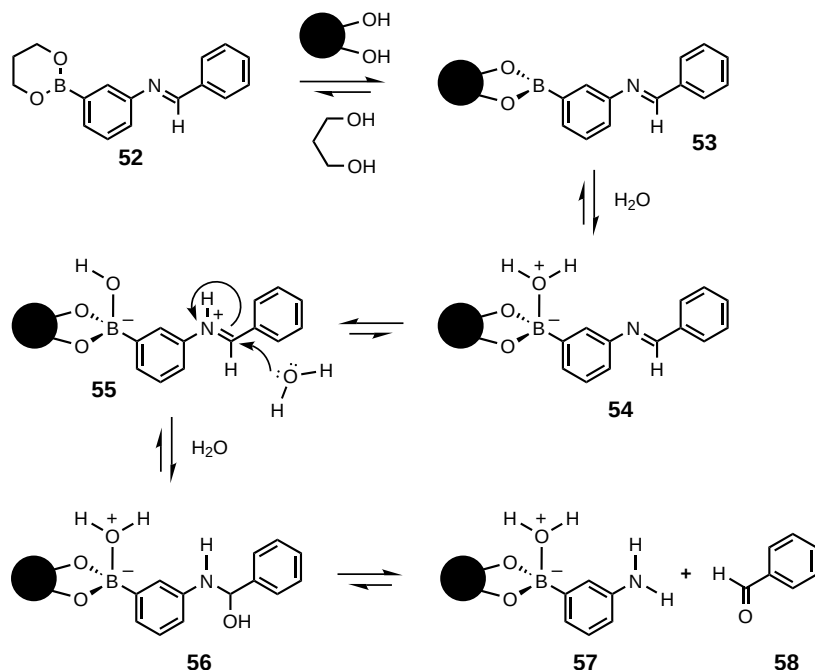


Figure 12. A free energy/reaction coordinate profile for the acid-catalyzed reaction of glycerol with isobutyraldehyde. Whereas the dioxanes are formed under thermodynamic control, the dioxolanes are obtained under kinetic control.

However, since the reaction is reversible and the six-membered (dioxane) ring compounds (*cis* and *trans* isomers) are more thermodynamically stable ($K > 1$), they become the major products in the course of time. Moreover, acid-catalyzed equilibration of the dioxolane/dioxane mixture proceeds via an oxycarbenium ion and does not necessarily need water. The equilibrium shifts toward the six-membered rings as the temperature is lowered because the entropy term favoring the more flexible five-membered ring becomes less important at lower temperatures. When cyclic acetals are formed between monosaccharides and either aldehydes or ketones in acidic media, molecular “acrobatics” occur in a really remarkable manner, thanks to dynamic covalent chemistry. For example, the acid-catalyzed reaction of ace-

tone with D-glucose gives 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose while essentially the same reaction performed on D-galactose affords 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose.

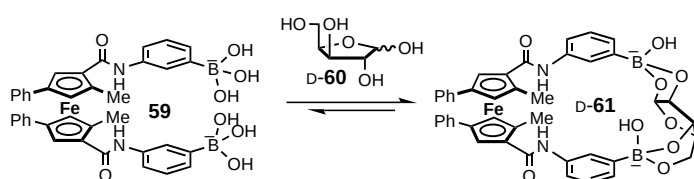
We now move on from the classic examples outlined above into a more contemporary setting, where we note that the ability^[84] of boronic acids to form cyclic esters reversibly upon reaction with diols has been utilized in many ways, and several reviews covering this topic have already been written.^[85] Most notably, the ability of boronic acids to recognize and discriminate between various carbohydrates and their derivatives has led to the creation of many novel saccharide sensors based upon photoinduced electron transfer^[86] or other^[87] signaling events. Here, we highlight two recent examples of the use of this dynamic covalent process in two different contexts. In 2000, Hartley and James^[88] reported an investigation into how the Lewis acidity of boronic acids/esters influences the rate of hydrolysis of simple imines (Scheme 23). Hydrolysis of imine **52** in a pH 7.77 buffer ($\text{H}_2\text{O}/\text{MeOH}$) was found to depend markedly upon the presence, if any, of a monosaccharide. It was found that there was a correlation between the rate of hydrolysis and the magnitude of the stability constant for borate ester formation: the stronger the interaction between the carbohydrate and the boronic acid, the faster the rate of hydrolysis. Hartley and James^[88] rationalized the observed trend in terms of the mechanism outlined in Scheme 23. Once the saccharide-based borate ester **53** is formed (in preference to the weaker 1,3-propanediol-derived one) a water molecule becomes more strongly bound to the Lewis acidic boron atom to generate intermediate **54**. At this pH value the “bound” water can act as an acid catalyst for the hydrolysis reaction, and a proton-transfer step occurs to give the iminium ion **55**, which is then attacked by water, and the hydrolysis proceeds via the intermediate **56** to give the aniline derivative **57** and benzaldehyde (**58**). A deuterium isotope study confirmed that



Scheme 23. The proposed mechanism to account for how the Lewis acidity of boronic acid/esters influences the rate of hydrolysis of simple imines.

the rate-determining step of the overall process involves a proton-transfer step. The authors conclude that the acid strength of the bound water molecule in intermediate **54** is influenced by the strength of its interaction with the borate ester, which, in turn, is modulated by the nature of the saccharide that is bound to the boronic acid. Therefore, the stronger the boronic acid/saccharide interaction is, the faster the imine hydrolysis will occur.

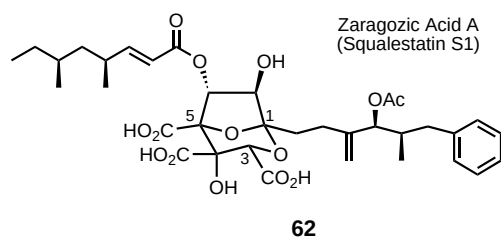
A chiral ferrocene derivative **59** adorned with two boronic acid derivatives was designed and synthesized by Shinkai and co-workers^[89] to act as a chiroselective saccharide sensor (Scheme 24). The diboronic acid **59** was found to exhibit some modest selectivity when binding D- and L-monosaccharides. The binding of D-xylose (**D-60**) to afford the derivative **D-61** is shown in Scheme 24. Association constants (K_D and K_L) were determined by monitoring the changes in the circular dichroism spectra as a function of the saccharide concentration, and the largest $K_L:K_D$ ratio of approximately 2.6:1 was observed in



Scheme 24. The proposed mode of binding of **D-60** by the diboronic acid receptor **59** to give the complex **D-61**.

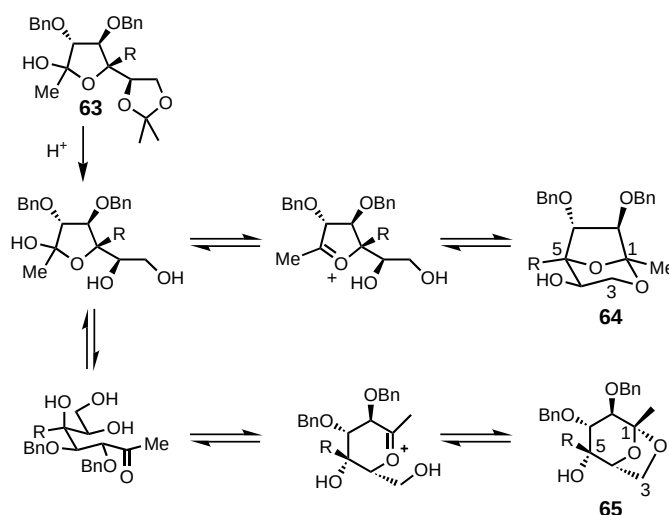
the case of mannose. Therefore, by employing a chiral scaffold together with dynamic covalent chemistry, it is possible to design and synthesize a molecule capable of binding different monosaccharide derivatives enantioselectively.

An example from the field of natural product synthesis, where dynamic chemistry has played an important role, is in the synthesis^[90] of the zaragozic acids **62** (squalostatins). The



zaragozic acids have shown promise as potent inhibitors of squalene synthase, which is the first pathway-specific step in the biosynthesis of cholesterol, and so have potential as therapeutic agents for the treatment of hypercholesterolemia. A key structural feature of zaragozic acids is the presence of a highly oxygenated core which contains a ketal, three carboxy, and two hydroxy groups. The presence of these functional groups makes it possible for transketalization to be used to help produce the complex bicyclic structure of **62**.

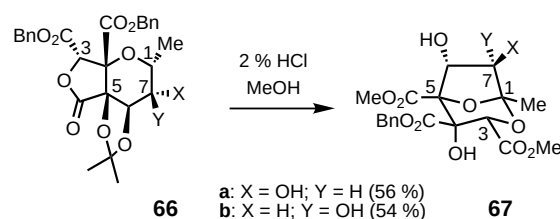
Some initial investigations on the dynamic synthesis of the zaragozic acids were carried out (Scheme 25) by Heathcock and co-workers.^[91] Treatment of the lactols **63** with acid



Scheme 25. Transketalization of **63**: Addition of 2 N HCl to **63** in THF results in the initial formation of **64** (the kinetic product), which can be interconverted to **65** (the thermodynamic product) given longer reaction times.

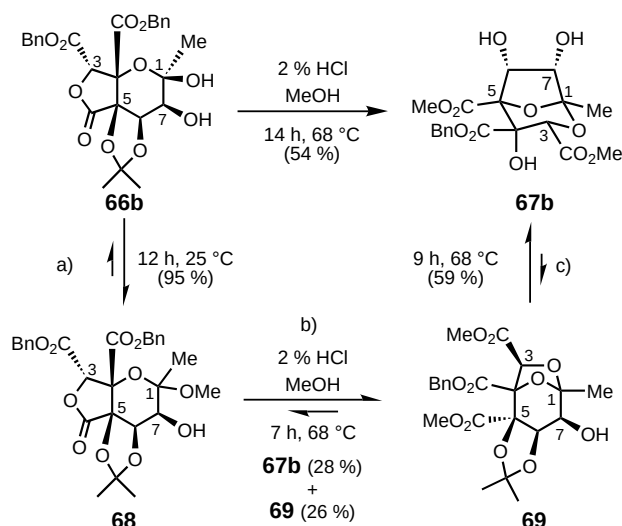
(2 N HCl, THF), followed by heating under reflux until the starting material had disappeared, resulted in high yields of the 1,5-dialkyl-1,6-anhydrofuranose **64**. This selectivity is subject to kinetic control. After longer reaction times, however, the amount of the 1,6-anhydropyranose derivative **65** increases. The final ratio of **64:65** at equilibrium depended on the nature of R. In general, the larger R is, the greater is the amount of **65** formed. Reversibility of the system was confirmed by resubmitting both **64** and **65** to the equilibration conditions, a procedure which resulted in ratios of **64** and **65** that were constant and reproducible. These results suggest that **64** is the kinetic product and that it equilibrates slowly to **65** under the reaction conditions.

Nicolaou et al.^[92] have utilized the dynamic synthesis of the zaragozic acid core as a key step in their total synthesis of this natural product. Heating **66a** or **66b** (the epimer at C-7) in 2% HCl/MeOH for 18 h at 68 °C resulted in a good yield of the desired bicyclic ketal **67a** or **67b**, respectively (Scheme 26). Two by-products were isolated from these

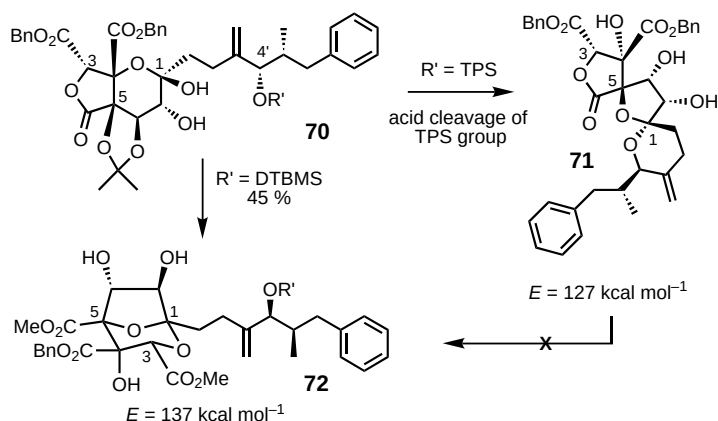


Scheme 26. Conversion of **66** into **67** upon treatment with 2% HCl in methanol.

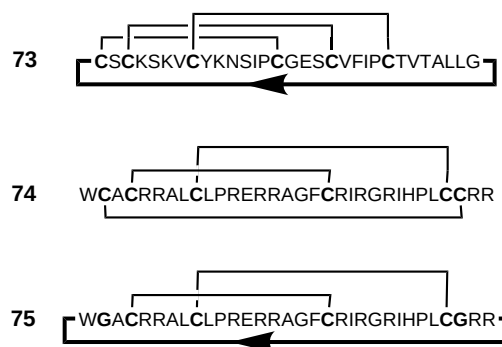
reactions, which did not go to completion. Treatment of lactol **66b** with 2% HCl/MeOH at room temperature for 12 h resulted in formation of the methyl glycoside **68** (Scheme 27). After 7 h at 68 °C, two major products were isolated: the desired bicyclic compound **67b** and the alternative [3.2.1] analogue **69**. Both **68** and **69** can be converted into the desired

Scheme 27. The pathway for the acid-catalyzed conversion of **66b** into **67b**.

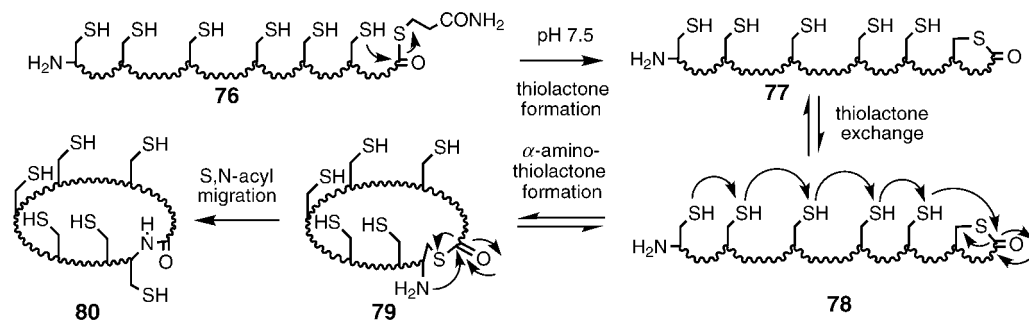
product **67b** by resubmitting them to the reaction conditions. These observations suggest that, in this system at least, the desired product is the thermodynamically more stable one. The formation of **67** as the more stable product at equilibrium is interesting, considering the results obtained by Heathcock and co-workers^[91] where it is the 1,6-anhydropyranose derivative **65** which is the more thermodynamically stable product. The difference in the product distribution in these two systems is probably a result of the different substitution patterns in the starting materials and thus in the products isolated. In order to complete the synthesis of the natural product, zaragozic acid A, the methyl group on C-1 needs to be replaced by the appropriate alkyl side chain (see compound **70**; Scheme 28). The side chain at C-1 of the natural product contains an acetylated hydroxy group at the C-4' position. If this hydroxy group is protected as the *tert*-butyldiphenylsilyl (TPS) group, then when compound **70** ($R' = \text{TPS}$) is subjected to the acidic equilibration conditions the TPS group is cleaved and the spiroketal **71**, and not the bicyclic compound **72**, is formed. Spiroketal **71** was shown by molecular modeling studies to be more thermodynamically stable than **72**. In support of the calculations, **71** did not rearrange further to **72** on being resubjected to the dynamic reaction conditions. However, if the C-4' hydroxy group is protected with the more acid-stable di-*tert*-butylmethylsilyl (DTBMS) protecting group, which is not cleaved under the reaction conditions, then the desired bicyclic compound **72** is formed.

Scheme 28. The acid-catalyzed rearrangement of the advanced intermediate **70** depends on the nature of the protecting group on the C-4' position (see text for more information).

The naturally occurring cyclic peptide cyclopsychotride **73** and the cyclic analogue **75** of the rabbit α -defensin **74**, in which the native end-to-end disulfide bond has been replaced,



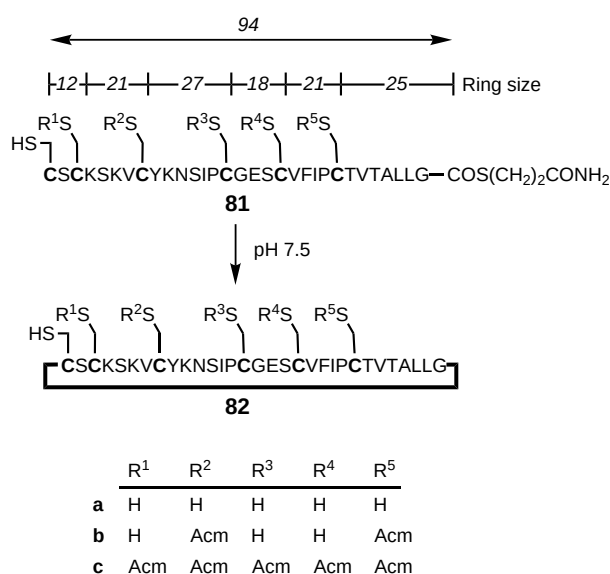
have been synthesized^[93] using a so-called zip reaction that involved reversible chemistry. Scheme 29 illustrates the proposed mechanism for this reaction, where a number of dynamic exchanges occur along the backbone of the molecule and results in the formation of a number of possible macrocyclic products. However, one product **79** can undergo an irreversible reaction which then traps the desired product. Thus, the dynamic chemistry in this system does not control the final product distribution but it does facilitate the formation of the kinetically stable macrocycle. In this particular example thiols from the cysteine residues along

Scheme 29. The proposed mechanism for the zip-reaction **76** $\rightarrow$ **80**.

the peptide backbone of **76** form successively a series of thiolactone intermediates (**77** and **78**) by stepwise ring expansions. The reversible equilibrations involving thiol–thiolactone exchanges will result eventually in partial formation of an *N*^α-aminothiolactone **79**. This intermediate can then undergo an irreversible ring contraction as a result of an S- to N-acyl transfer, thus providing the driving force for the zip reaction which results in the end-to-end lactam **80**.

The zip reaction differs from more conventional macrocyclizations in that the latter are generally disfavored on account of the entropic penalty involved in the formation of large rings. By contrast, the zip cyclization involves a series of intramolecular rearrangements of smaller rings that ends with irreversible S,N-acyl migration at the α -amino terminus to afford the desired macrocycle. As a result, the zip-assisted cyclization is entropically more efficient than the corresponding one-step end-to-end cyclization. In addition, the intrinsic high effective molarities of the intramolecular reactions mean that the proposed zip reaction has the advantage of reducing the chance of oligomerization of the monomeric species.

The linear analogue of **73** contains five internal thiol units that can be used to form intermediate thiolactones. The cyclizations of a series of linear peptides with varying numbers of the thiol groups protected with the acetamidomethyl group (Acm) were carried out to examine the roles of these thiol residues in the thiolactone zip reactions (Scheme 30). The



Scheme 30. The cyclizations of linear peptides **81a–c** with varying numbers of Acm-protected thiol groups to yield the cyclic peptides **82a–c**.

rates of cyclization of the three derivatives were determined (Table 3) under physiological conditions (0.2 M phosphate buffer). The rate of cyclization of the zip-assisted reaction of **81a** is very rapid ($t_{1/2}$ = 0.3 h) while that of the unassisted cyclization of **81c**, with all five internal thiols protected, is around seven times slower ($t_{1/2}$ = 2.0 h). Even so, this unassisted reaction is still fast for the formation of a macrocycle containing 93 atoms, presumably on account of the linear peptide chains adopting conformations that hold the N and C termini in proximity. The cyclizations were then carried out

Table 3. Zip-assisted cyclization of CT **81a** and CT-2Acm **81b**, as well as direct cyclization of CT-5Acm **81c** under non-denaturing (aqueous) and denaturing (8 M urea) conditions.

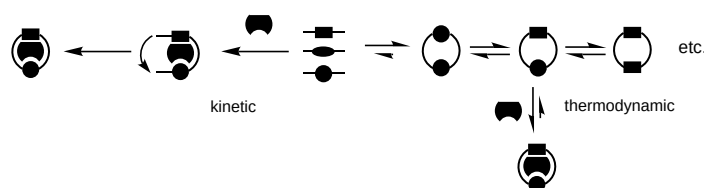
Peptide	Internal free thiol groups	Ring atoms		$t_{1/2}$ for cyclization [h]	
		thiolactone intermediate	lactam product	aqueous	8 M urea
CT 81a	5	12–27	93 (82a)	0.3	0.6
CT-2Acm 81b	3	18–40	93 (82b)	0.9	2.6
CT-5Acm 81c	0	94	93 (82c)	2.0	120.0

under denaturing (8 M urea solution) conditions to impair this conformational assistance. The zip-assisted cyclizations of **81a** (five internal thiols) and **81b** (three internal thiols) require 0.6 and 2.6 h, respectively, for 50 % conversions to the corresponding lactams **82a** and **82b**. By contrast, the unassisted cyclization of **81c** was 200 times slower than for **81a**, requiring 120 h for 50 % conversion. The synthesis of the natural product **73** is completed by the stepwise formation of two disulfide bonds. Compound **82b**, which contains four unprotected thiols, yields all three possible isomers in about equimolar amounts upon reaction in an aqueous media containing 10 % DMSO. After isolation of the desired isomer, cleavage of the Acm protecting groups, and disulfide formation with I₂ in methanol at pH 4, the cyclic peptide **73** was isolated in an overall yield of 15 % starting from **82b**.

Transesterification can also be used in the synthesis of natural products. For example, Gutierrez and co-workers have reported^[94] an improved synthetic procedure to enterobactin and enantioenterobactin where a transesterification reaction is used as the key step.

3.2. Macrocyclic Compounds

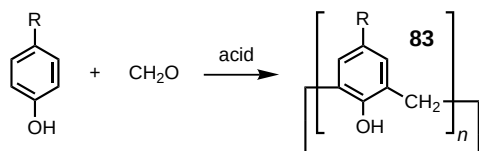
Since macrocyclizations carried out under kinetic control are generally low-yielding reactions, which result in the formation of a wide range of cyclic oligomers and/or polymers,^[95] the prospect of being able to self-assemble macrocycles efficiently under thermodynamic control is extremely attractive. Generally, synthetic chemists have resorted to the use of a variety of different measures, such as templating and high-dilution techniques, to favor the formation of particular macrocycles through kinetically controlled macrocyclizations. High dilution (see Section 2.2) and/or templating can also be used to induce the formation of macrocycles under thermodynamic control. However, there is an important distinction (Scheme 31) to be made between



Scheme 31. A schematic representation illustrating the difference between kinetic and thermodynamic templating in the formation of macrocycles.

kinetic and thermodynamic templating in relation to macrocycle formation. In kinetic templating, the template binds a linear species, which brings the two chain ends into proximity, thus resulting in an increase in the rate of ring formation for a particular macrocycle. By contrast, in thermodynamic templating, the template binds to the macrocycle itself and forms a complex which stabilizes the macrocycle. This situation results in an equilibrium involving a range of different macrocycles becoming biased toward the formation of one particular macrocycle.

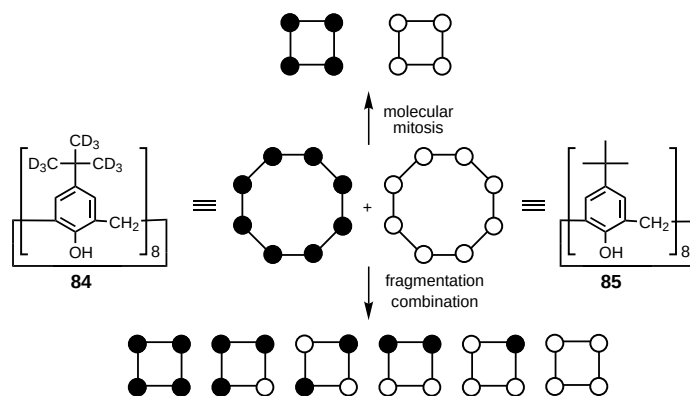
The use of dynamic chemistry to prepare macrocycles is by no means new. The syntheses of macrocycles prepared from π -electron-rich aromatic compounds and aldehydes or ketones have been shown to have reversible traits. For example, the reaction^[96] of *p*-substituted phenols with formaldehyde in the presence of either acid or base yields the basket-shaped molecules known as calix[*n*]arenes **83** (Scheme 32).^[96, 97] Experiments have demonstrated that the cyclic octamer, calix-[8]arene, which can be isolated as the kinetic product under



Scheme 32. Synthesis of calix[*n*]arenes **83** from *p*-substituted phenols and formaldehyde.

relatively mild reaction conditions, can be converted, in greater than 75 % yield, into the thermodynamic product in the form of the cyclic tetramer, calix[4]arene, when the cyclic octamer is subjected to high temperatures. These same conditions also yield the calix[4]arene directly from formaldehyde and the phenol derivative. There have been two mechanistic pathways proposed to explain this conversion. In the first pathway, which is called^[98] “molecular mitosis”, the calix[8]arene breaks into two tetrameric components which then cyclize independently to yield the calix[4]arene. A second possible pathway involves a fragmentation of the calix[8]arene into smaller oligomeric units, followed by their recombination to yield the thermodynamically more stable calix[4]arene. In a recent publication, Gutsche et al.^[99] examined this “reversible reaction” using the deuterated *p*-*tert*-butylcalix[8]arene **84** and ordinary *p*-*tert*-butylcalix[8]arene **85** (Scheme 33). Treatment of both of these calix[8]arenes with sodium hydroxide in boiling diphenyl ether resulted in the formation of all six possible calix[4]arenes as indicated by mass spectrometry (Figure 13). This observation suggests that the major reversible process is the fragmentation/recombination pathway.

A similar kind of reversible chemistry has also been demonstrated in the synthesis of the related resorcinarene macrocycles **86**. Although the reaction of aldehydes (such as benzaldehyde) with resorcinol can lead to a number of different products, only two are observed during the course of their reaction in an acidic ethanolic solution (Scheme 34): **86**-*C*_{4v} (R = Ph) and **86**-*C*_{2v} (R = Ph). The *C*_{2v} isomer is the kinetic product and is formed faster than the *C*_{4v} isomer, the



Scheme 33. Two potential pathways for the formation of *p*-*tert*-butylcalix[4]arene from **84/85**.

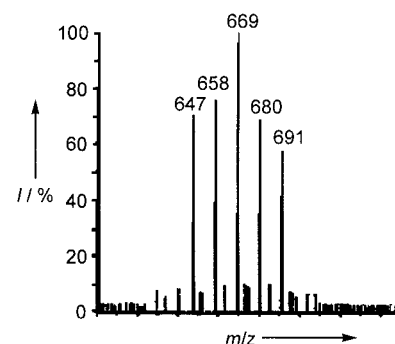
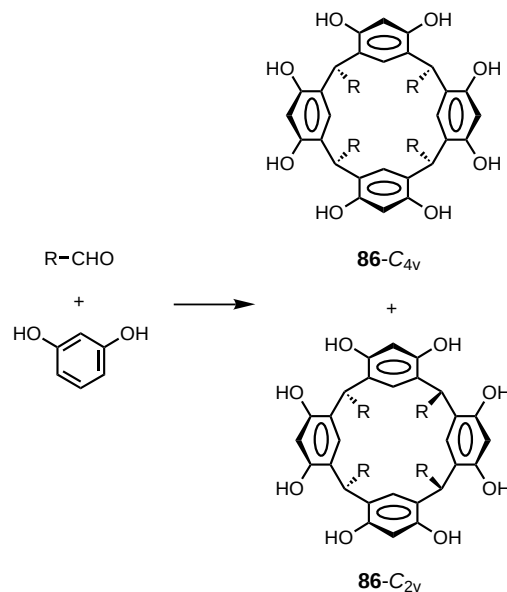


Figure 13. Mass spectrum of *p*-*tert*-butylcalix[4]arene obtained from a reversible reaction of a 1:1 mixture of **84** and **85**.



Scheme 34. Reaction of resorcinol with aldehydes under acidic conditions results primarily in the formation of the *C*_{4v} and *C*_{2v} isomers of **86**.

thermodynamic product. Over a period of time, however, the initial kinetic product is slowly converted into the thermodynamic one (Figure 14). Cram and Cram^[100] have investigated the synthesis of a large number of resorcinarene derivatives and have attributed the stereoselectivity shown in their synthesis to several factors: 1) the *C*_{4v} isomer is the most insoluble product formed during the series of reversible

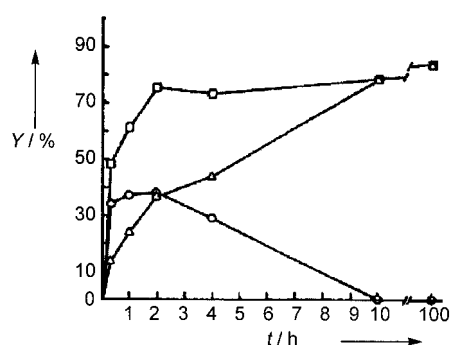
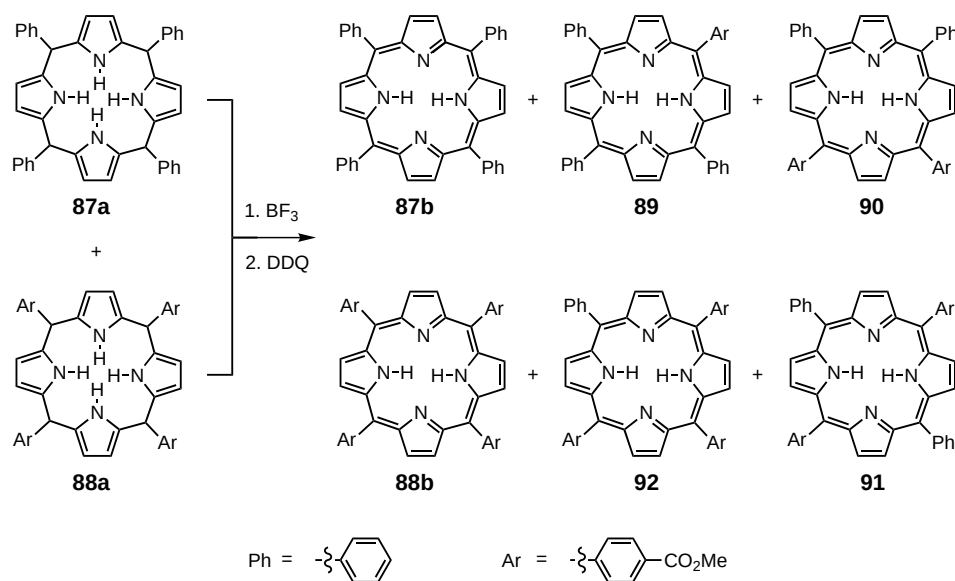


Figure 14. Product distribution as a function of time for the reaction of resorcinol (1.0M) and benzaldehyde (1.0M) in a mixture of ethanol and concentrated HCl (4:1) at 75°C. □: total yield, △: yield of C_{4v} isomer, ○: yield of C_{2v} isomer.

reactions, a characteristic which results in it crystallizing from the medium and so driving all reactions toward the formation of this isomer; and 2) the condensation medium is hydrophilic and so, in reactions where the R group is a long aliphatic chain (for example, $R = \text{Me}(\text{CH}_2)_{10}$) the C_{4v} configuration—with all four R groups adopting axial orientations—is the only one that allows these lipophilic moieties to come into contact with one another and constitute stabilizing hydrophobic interactions.

Porphyrinogens, which are formed by the reaction of aldehydes with pyrroles, can also be prepared under thermodynamic control. The synthesis of the *meso*-tetraaryl porphyrins involves two steps: 1) the reversible reaction of benzaldehydes with pyrrole to yield a porphyrinogen, followed by 2) oxidation of the porphyrinogen (for example, with *p*-chloroanil or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)) to yield the kinetically stable porphyrin macrocycle; this second reaction can essentially be considered a fixing step.

Lindsey et al.^[101] have investigated the reversible steps in porphyrin syntheses with the aim of optimizing the yields of the products obtained in this reaction. The reversibility of the porphyrinogen syntheses was demonstrated through exchange experiments. In one example, tetraphenylporphyrinogen **87a** and tetrakis[4-(methoxycarbonyl)phenyl]porphyrinogen **88a** were prepared in separate reaction vessels, before being added together and allowed to react for a further two hours in the presence of an acid catalyst (Scheme 35). The outcome (Table 4) is approximately the statistically expected ratio of all six tetrameric species. The same distribution is obtained if equimolar amounts of benzaldehyde and methyl 4-formylbenzoate are condensed simultaneously with a stoichiometric amount of pyrrole. It is interesting to note that the reaction leading to tetraalkylporphyrinogens was shown not



Scheme 35. The six porphyrin products **87b**–**92** observed after mixing preformed solutions of **87a** and **88a** in the presence of BF_3 , followed by oxidation of the reaction mixture with DDQ.

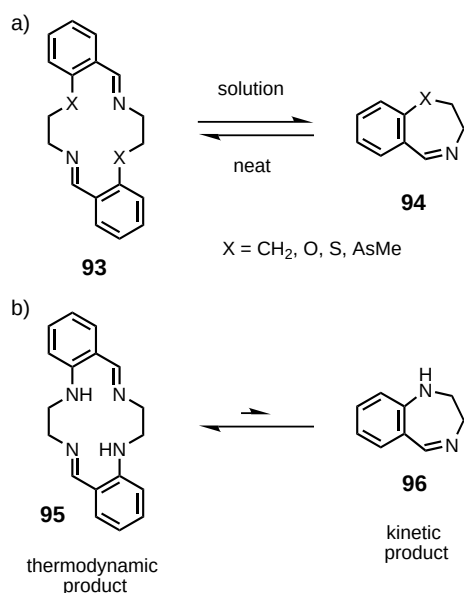
Table 4. Yield [%] of the resulting porphyrins, **87b** and **88b** and **89**–**92**, obtained after oxidation (DDQ) of the porphyrinogen mixing experiments.

	87b	89	90	91	61	88b
before exchange	42.0					48.8
after exchange ^[a]	7.3	24.6	23.2	11.6	20.5	12.8
mixed condensation ^[b]	6.8	22.4	24.6	13.0	25.8	7.4
statistical expectation	6.25	25	25	12.5	25	6.25

[a] “After exchange” is the distribution obtained 2 h after combining preformed and separate solutions of porphyrinogens **87a** and **88a**. [b] “Mixed condensation” is the porphyrinogen distribution when equimolar quantities of benzaldehyde and methyl 4-formylbenzoate were simultaneously condensed with a stoichiometric amount of pyrrole.

have revealed selective product distributions, even without the presence of a metal ion. However, since irrefutable evidence that these macrocycles are indeed formed under thermodynamic control has not been presented, this topic will not be covered here.

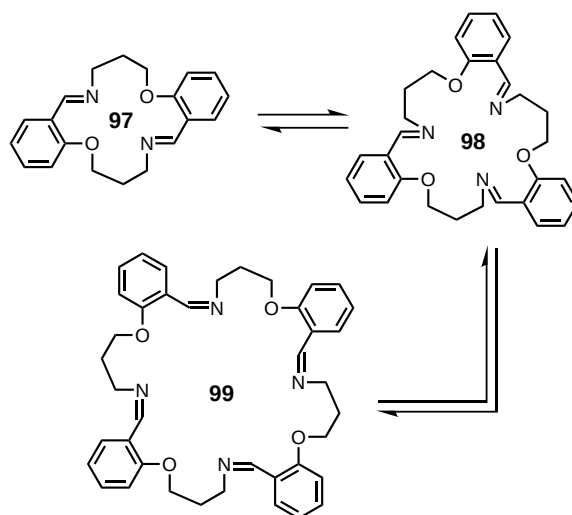
Wild and his research group^[105] have examined a number of imine-containing systems which demonstrate reversible characteristics (Scheme 36). The 14-membered diimine macro-



Scheme 36. a) The 14-membered diimine macrocycle **93** and the monomer **94** interconvert under acidic conditions. In solution (for example, CHCl₃), **94** is favored while the dimer **93** is favored when neat. b) The monomer **96** can be isolated as the kinetic product. However, when it is dissolved in DMSO, it reverts to the thermodynamically more-stable 14-membered diimine macrocycle **95**.

cycles **93** can be prepared in high yields in the absence of templating metal ions. It was shown, for X = CH₂, O, S, or AsMe, that the monomer **94** is favored in solution and that the dimer **93** can be isolated as a crystalline solid by removal of solvent from the monomer solution. However, when X = NH dimer **95** has been shown to be the thermodynamic product in solution. The seven-membered-ring monomer **96** can be isolated as the kinetic product, a property which was demonstrated by this monomer being slowly converted into the dimer **95** in DMSO. The addition of more flexibility into the monomer by the incorporation of another methylene unit between the heteroatoms resulted in the formation of a more diverse range of large macrocycles with the dimer ($n=2$), trimer ($n=3$), and tetramer ($n=4$) all being observed. The corresponding monomer was not observed, presumably because it would be a thermodynamically unfavorable eight-membered ring. The exchange process (Scheme 37) for the oxygen-containing imine macrocycles **97** (dimer), **98** (trimer), and **99** (tetramer) in CDCl₃ was monitored by ¹H NMR spectroscopy. The half-lives for the conversions of the dimer and tetramer into equilibrium mixtures of dimer, trimer, and tetramer were measured and found to be about 7 and 10 minutes for the dimer and tetramer, respectively. The relative proportions of the three macrocycles was also found to be concentration dependent in chloroform (Figure 15). Although the dimer **97** is the dominant product at low concentrations (at 0.006 M, **97:98:99** = 72:23:5), the amount of the dimer **97** decreases concurrently with an increase in the amount of the tetramer **99** at higher concentrations (at 0.2 M, **97:98:99** = 44:31:25).

Corey et al.^[106] investigated the use of a reversible transesterification process to synthesize macrocyclic lactones using a ring-expansion protocol (Scheme 38). The “smaller” lactone



Scheme 37. The interconversion of the imine macrocycles **97**, **98**, and **99**.

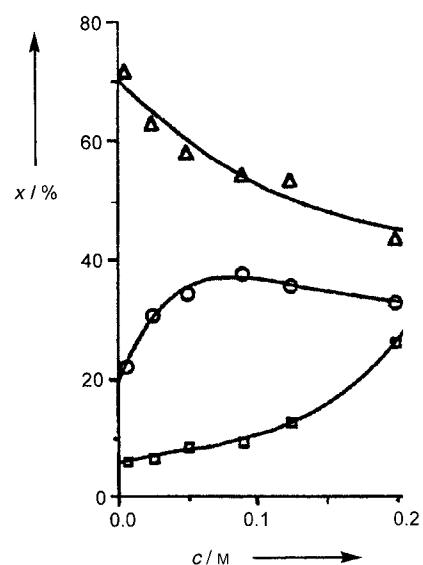
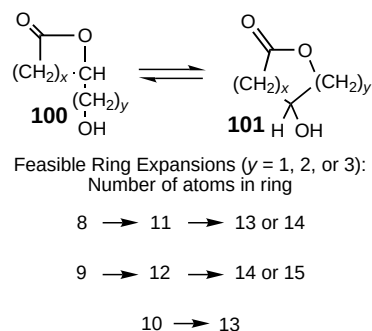


Figure 15. Relative equilibrium proportions (x) of imine macrocycles **97**, **98**, and **99** in CDCl₃ solution as a function of the equivalent concentration c of the imine. (Δ : **97**, $\circ$: **98**, $\square$: **99**).

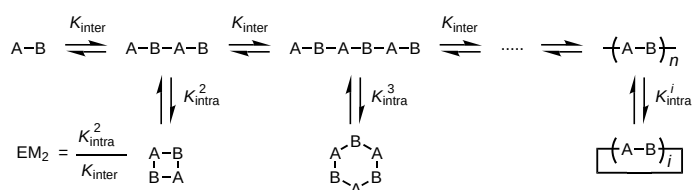


Scheme 38. Synthesis of the macrocyclic lactones **101** using a ring-expansion protocol.

100 was submitted to equilibrating conditions (1–3% *p*-toluenesulfonic acid in CH₂Cl₂ at room temperature) in an attempt to yield the “larger” lactone **101**. Their studies demonstrated that strained, medium-sized-ring lactones can

be converted into larger less-strained macrocycles. Eight-membered-ring lactones (**100**, $x = 5$) can be converted into 11- (**101**, $y = 3$), 13- (**101**, $y = 5$), and 14-membered-ring (**101**, $y = 6$) lactones, while nine-membered ring lactones (**100**, $x = 6$) can be converted into 12- (**101**, $y = 3$), 14- (**101**, $y = 5$), and 15-membered-ring (**101**, $y = 6$) lactones and that 10-membered-ring lactones (**100**, $x = 7$) can be converted into 13-membered-ring (**101**, $y = 3$) lactones. The smaller, more thermodynamically favorable seven-membered-ring lactone (**100**, $x = 4$) does not form the corresponding 10-membered-ring compound and only undergoes partial conversion (65 %) into the 11-membered-ring compound under equilibration conditions.

Macrocyclization can be regarded essentially as a polymerization carried out under dilute conditions. A theoretical treatment of thermodynamic cyclizations based on the Jacobson–Stockmayer theory for equilibrium polymerizations (see Section 2) has been described by Ercolani et al.^[107] The theory predicts that the distribution of cyclic oligomers in the thermodynamic cyclization of flexible monomers is dependent on two major factors (Scheme 39): 1) the monomer concentration expressed as the intermolecular equilibrium constant K_{inter} and 2) the effective molarity^[108] of cyclization $K_{\text{intra}}^i/K_{\text{inter}}$. Basically, it predicts that, as the monomer concentration is raised, an increase in the size of the rings



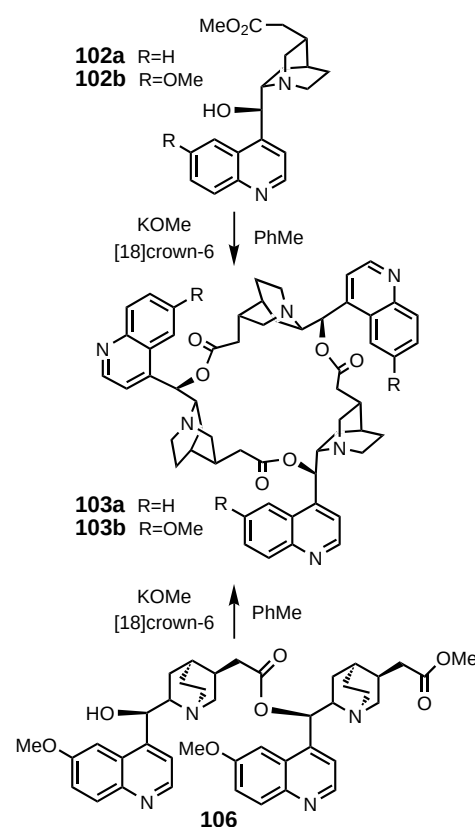
Scheme 39. Equilibrium processes involved in the synthesis of dynamic macrocycles.

formed is observed until the critical monomer concentration is reached, above which polymers start to be formed. However, according to this theoretical treatment, the critical monomer concentration is only present if the intermolecular equilibrium constant K_{inter} is large, a situation which is required anyway for the formation of polymers. If K_{inter} is small, then acyclic material will be observed at all concentrations. This fact has the important consequence that K_{inter} has to be large for the efficient formation of macrocycles as well as of polymers.

Ercolani^[109] has recently developed this theory for the self-assembly of macrocycles using rigid monomers. If the self-assembly of a predisposed building block is to yield mainly one cyclic species, then there are two main criteria that are required to ensure effective synthesis of the desired cyclic i macrocycle (for example, the dimer ($i = 2$)). The first condition is that the formation of the cyclic dimer must have a much larger effective molarity (EM_2) than all of the other macrocycles. The second theoretical condition states that the product $EM_2 K_{\text{inter}}$ must not be lower than $185r$, where r is the number of dynamic bonds holding the cyclic species together ($r = 2$ for a cyclic dimer). In general, both of these conditions can be attained by building into the monomer rigidity that will

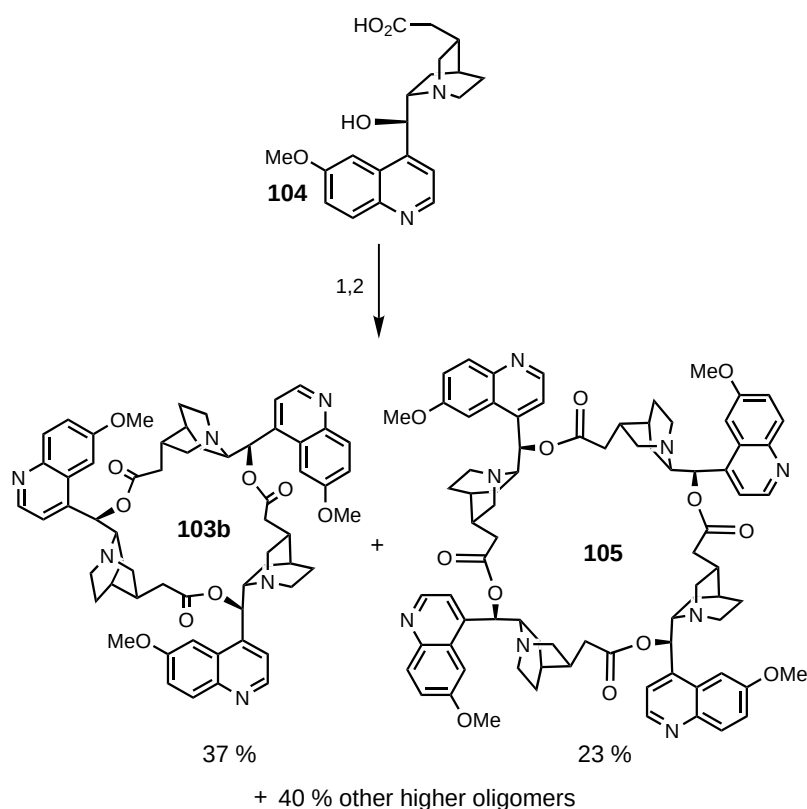
favor the formation of dimer (by increasing EM_2) while hindering the formation of other cyclic oligomers.

The ability to be able to form selectively only one macrocyclic species under thermodynamic control was recently demonstrated for a number of monomers containing both hydroxy and ester functional groups. By utilizing transesterification as the reversible covalent bond forming step, the hydroxyester monomers were submitted to thermodynamically controlled cyclization conditions (5 mM, 5% KOMe/[18]crown-6/PhMe and heating under reflux). Both the cinchonidine- and quinine-derived monomers (**102a** and **102b**, respectively) form selectively the cyclic trimers (**103a** and **103b**, respectively) in > 90 % yield (Scheme 40).^[110] A comparison was made with the analogous kinetic cyclization



Scheme 40. Thermodynamic cyclization of the monomers **102a** and **102b** (5 mM) results almost exclusively in the formation of cyclic trimers **103a** or **103b**, respectively. Cyclization of the linear dimer **106** (5 mM) also results in the formation of cyclic trimer **103b** under thermodynamic control.

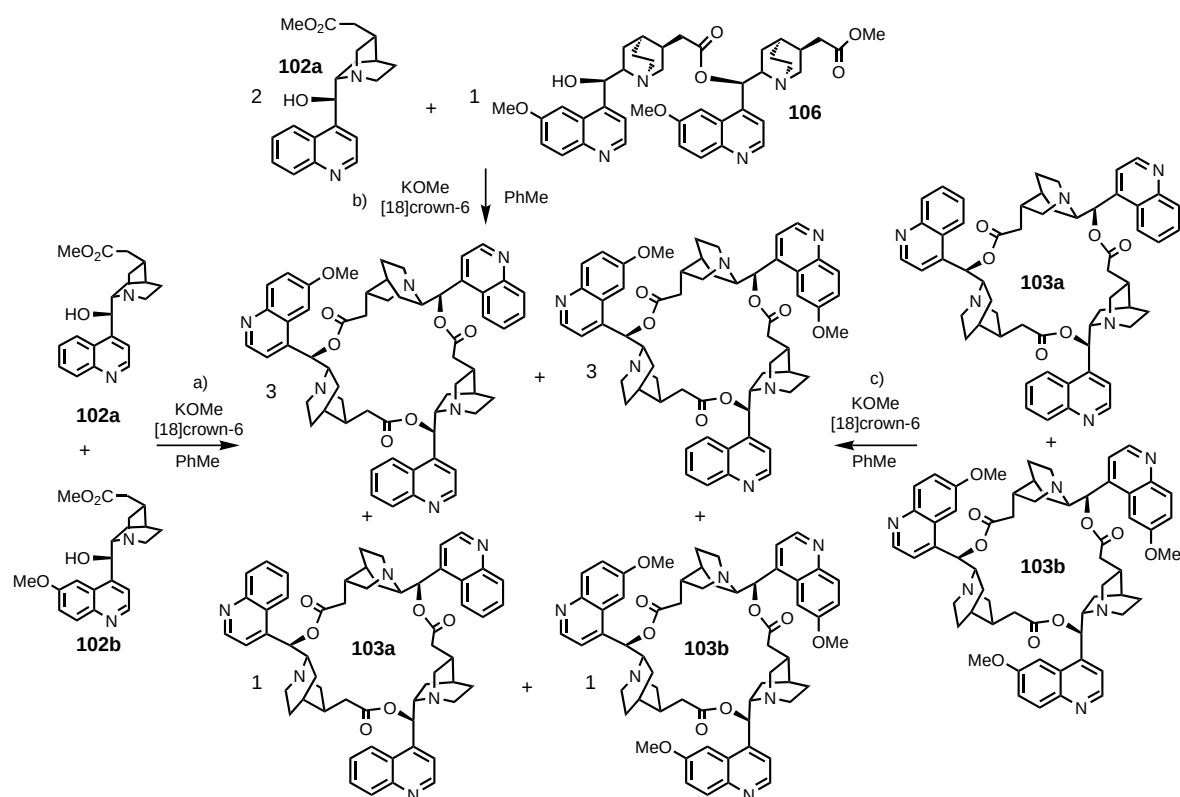
to demonstrate the importance that the reversible nature of the reaction has on the selectivity exhibited during this cyclization process. This was achieved by submitting the hydroxy acid **104** (5 mM) to irreversible macrolactonization conditions (Scheme 41).^[111] A much broader distribution of products was obtained from the kinetically controlled reaction. Although the main product was still the cyclic trimer **103b** (as in the case of the thermodynamic reaction) it was present in a greatly reduced quantity (37% based on the monomer). Another 23% of the monomer formed the tetramer **105**, with the remainder affording higher oligomers, at least as indicated by ¹H NMR spectroscopy. Of course, if a



Scheme 41. Kinetic cyclization of monomer **104** (at 5 mM) results in a mixture of cyclic oligomers. 1) 2,6-Dichlorobenzoyl chloride, Et_3N , DMF; 2) 4-dimethylaminopyridine, CH_2Cl_2 , RT.

reaction is truly dynamic then the product distribution should still be the same, no matter what oligomer is used as the starting material. To test this premise the linear dimer **106** was synthesized and subjected to the thermodynamic cyclization conditions. Once again, the cyclic trimer **103b** was obtained in high yield (Scheme 40).

Further proof was obtained that this cyclization is truly reversible by carrying out a series of mixing experiments with cinchonidine and quinine oligomers. Reacting together either both monomers **102a** and **102b** (Scheme 42a), or one monomer **102a** with the linear dimer **106** (Scheme 42b), resulted in a statistical 1:3:3:1 ratio of four possible trimers containing 0, 1, 2, and 3 methoxy groups, respectively, as indicated by electrospray mass spectrometry (ESMS). These experiments confirm that the cyclic trimers are the thermodynamically favored products. The preformed cinchonidine and quinine cyclic trimers **103a** and **103b**, respectively, were submitted to the thermodynamic reaction conditions to determine just how thermodynamically stable the cyclic trimers are and to prove that they can be opened up and then broken down into smaller units (Scheme 42c). The result is identical to that obtained from the previous mixing experiments wherein all four possible trimers are present in a 1:3:3:1 ratio (ESMS; Figure 16). This result is consistent only with the reversible breakdown of



Scheme 42. Mixing experiments used to examine the reversibility of macrolactonization. a) Mixing of the two monomers **102a** and **102b**. b) Mixing of two equivalents of monomer **102a** with one equivalent of linear dimer **106**. c) Mixing of **103a** and **103b**. All three reactions, which were carried out at [repeat unit] = 5 mM, yield the same product distributions (1:3:3:1) of the four possible cyclic trimers.

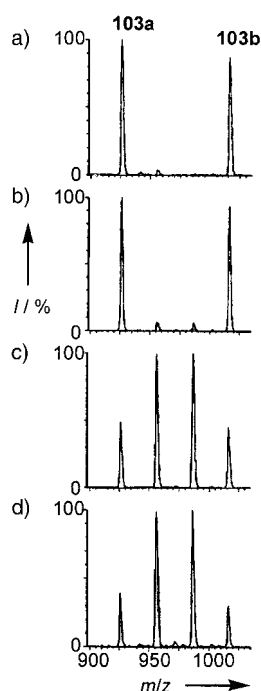
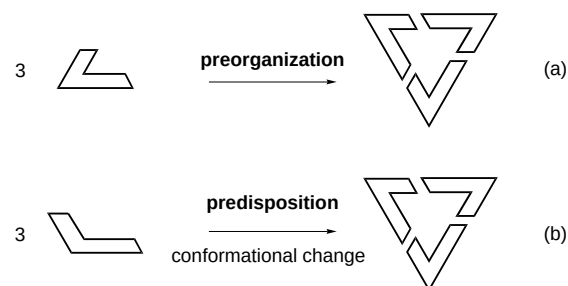


Figure 16. Molecular ion region of the ES mass spectra of the mixed reaction of **103a** and **103b**: a) The reaction mixture before any catalyst was added, b) after 20 s, c) after 2 min, and d) after 10 min. The four peaks correspond to trimers with zero (m/z 925, $[M + H]^+$), one (m/z 955, $[M + H]^+$), two (m/z 985, $[M + H]^+$), and with three 6'-OMe groups (m/z 1015, $[M + H]^+$). The deviation from the expected 1:1 peak intensities in (a) and from 1:3:3:1 in (c) results mainly from the slight excess of **103b** used (1.03×10^{-5} mol) compared to that of **103a** (9.7×10^{-6} mol).

the initial homotrimers and the subsequent formation of heterotrimers, in addition to the homotrimers. The heterotrimers appear almost immediately (20 s) and there is already a heterotrimers:homotrimers ratio of about 2:1 after only 2 min. The statistically expected 3:1 ratio is reached within 10 min and persists thereafter indefinitely.

The thermodynamic preference for the formation of the cyclic trimer has been attributed to a property we refer to as the predisposition of the monomer units. The term predisposition must be distinguished carefully from another term, namely preorganization. This latter term generally refers to the ground state of the monomer, whose conformation holds the reactive groups in proximity, thereby favoring one pathway (Scheme 43a) over all the other alternatives. Preorganization in covalent chemistry is best regarded as a kinetic



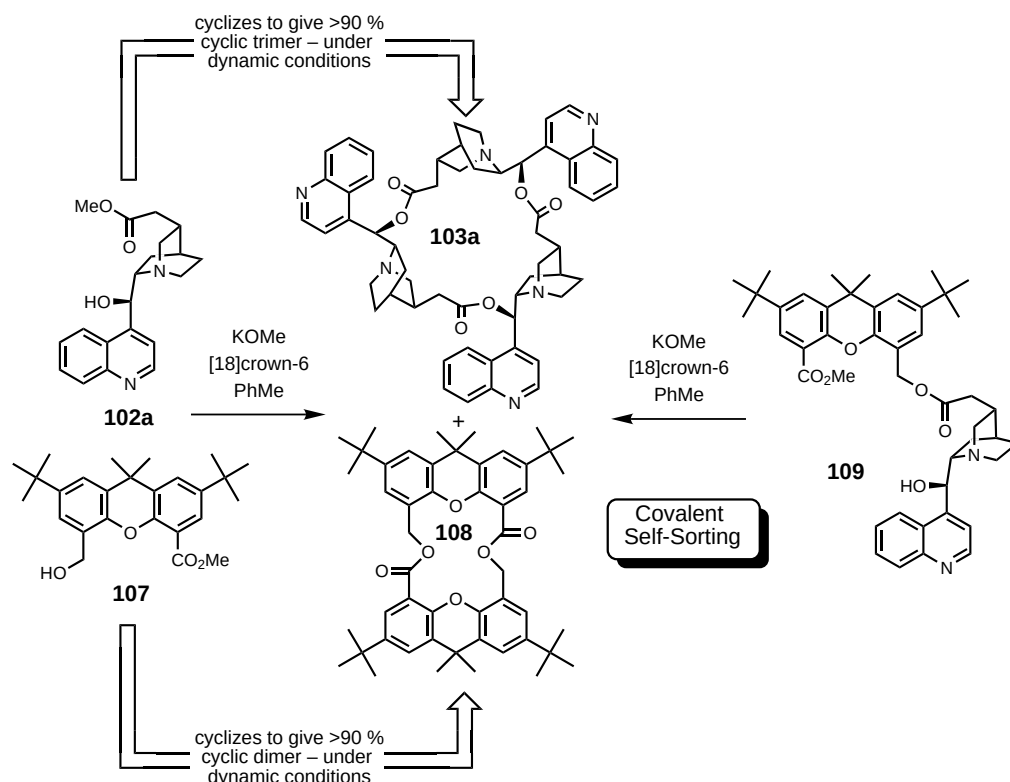
Scheme 43. Schematic representation of a monomer preorganized (a) and predisposed (b) to form a cyclic trimer.

process. Predisposition, on the other hand, should be thought of as a strong conformational or structural preference expressed by the building block once incorporated into a larger structure, which gives rise to a thermodynamic preference for a particular product (Scheme 43b). This statement implies that the final conformation in the oligomer (cyclic trimer in this case) is not the same as, or dictated by, the ground-state conformation of the free monomer.

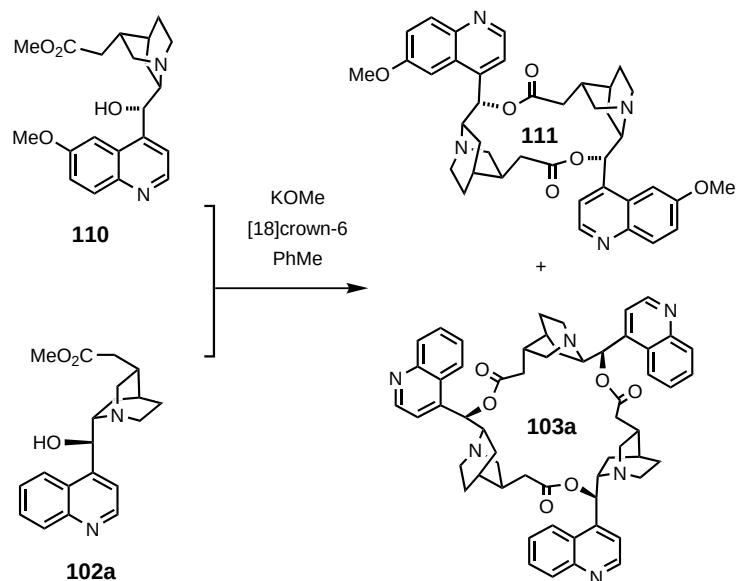
To examine just how strong is the predisposition of the cinchona alkaloid monomer **102** to form the cyclic trimer, we examined^[112] its thermodynamic cyclization (Scheme 44) in the presence of the preorganized xanthene monomer **107**. This xanthene monomer forms its own cyclic dimer **108** in >90 % yield when it is subjected to the equilibration conditions by itself. When a mixture of the cinchonidine and xanthene monomers, **102a** and **107**, respectively, are cyclized under thermodynamically controlled reaction conditions, very little of the mixed oligomers are observed; the homo-cinchonidine trimer **103a** and the homo-xanthene dimer **108** are the major products. This reaction is an example of a covalent self-sorting process wherein the thermodynamic driving force for the self-sorting is the relative stability of the homomeric species compared to the heteromeric species. This self-sorting process was probed further by synthesizing the mixed linear dimer **109** and submitting it to the dynamic conditions. As expected for a reversible reaction, an identical product distribution to that obtained starting with the monomer was observed. This reaction demonstrates the proof-reading ability of dynamic chemistry, that is, if the reactants come together in an “incorrect”, thermodynamically unfavorable manner then the system can and will readjust to yield the thermodynamically favored products.

The effect of introducing a major shape change into the cinchona alkaloid monomer on the thermodynamic macrocyclization has also been examined.^[113] The methyl ester of quinidine, which has inverted stereochemistry (relative to the quinine derivative) at the C-8 and C-9 positions, but not at the C-3 position, was expected to lead to a different product distribution of macrocyclic products. Monomer **110** was cyclized under conditions of thermodynamic control to yield almost exclusively the cyclic dimer **111** with up to 5 % of the cyclic trimer also observable by both the ESMS and by HPLC. This experiment indicates that it should be possible to initiate the efficient synthesis of a desired macrocyclic oligomer by preprogramming the shape of the monomer. When the cinchonidine and quinidine monomers **102a** and **110**, respectively, are cyclized together, they self-sort into the cinchonidine cyclic trimer **103a** and quinidine dimer **111** (Scheme 45). Although this experiment constitutes another example of covalent sorting, it can also be thought of as an example of the self-sorting of diastereoisomers—a stereochemical consequence that emphasizes the importance of shape in thermodynamic chemistry.

Reversible olefin metathesis chemistry has recently been shown by Smith et al.^[114] to also selectively yield one macrocyclic product even though a number of possible macrocycles are potentially accessible. Cyclization of the diolefin **112**, with the active Schrock catalyst **3**, yields macrocyclic dimer **113** in 72 % yield (Scheme 46), even though there are seven different

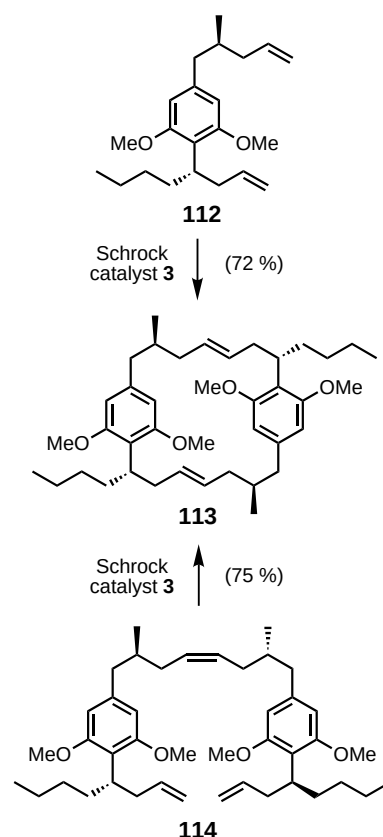


Scheme 44. Demonstration of self-sorting at the covalent level: **102a** and **107** yield selectively the homocyclic trimer **103a** and dimer **108**, respectively, under thermodynamic cyclization conditions (at 5 mM). The major products obtained upon mixing the two monomers are still the homocyclic species. The same product distribution is also observed when the heterolinear dimer **109** is subjected to the equilibrating conditions.



Scheme 45. Covalent self-sorting of diastereoisomers: Subjecting monomers **110** and **102a** to the dynamic reaction conditions results in the formation of the homodimer **111** and the homotrimer **103a**.

cyclic dimers possible from the cyclization of **112**. Molecular modeling studies confirmed that the [7,7]-(*E,E*)-paracyclophane **113** has the lowest energy structure of all the possible isomers and suggests that this reaction is indeed under thermodynamic control. To confirm that the olefin metathesis reaction is reversible in nature during this reaction triene



Scheme 46. Selective formation of the macrocycle **113** from either **112** or **114** by reversible olefin metathesis.

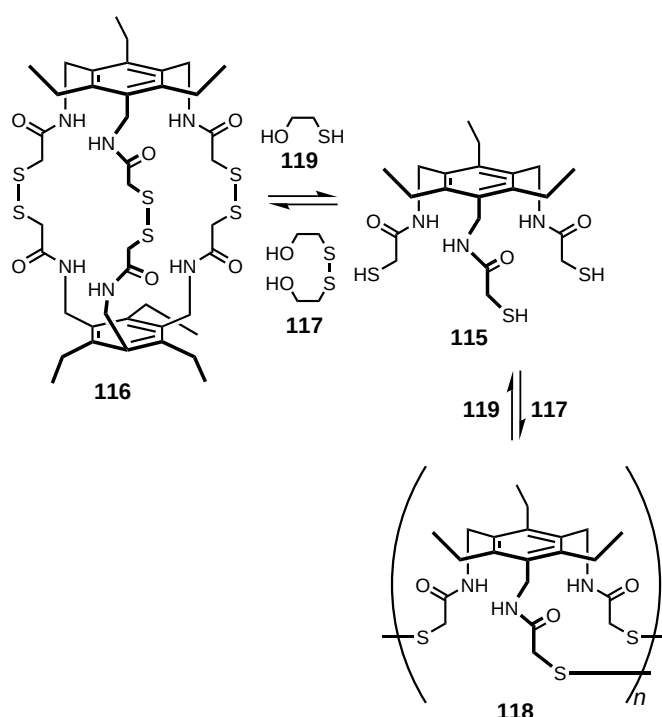
114, which is preorganized to form the [8,6]-paracyclophane, was synthesized. However, the formation of the cyclic dimer **113**, in high yield, was observed upon subjecting **114** to the reaction conditions. Presumably a cascade of reversible olefin metathesis reactions result in the formation of the thermodynamically most stable product.

3.3. Molecular Capsules

The design and construction of container-like molecules and supermolecules has attracted a considerable amount of interest in recent years.^[115] In general, most examples are either noncovalently bonded assemblies^[116] (supermolecules) of complementary components, or wholly covalent structures^[117] (molecules) that have been constructed under kinetic control.^[118]

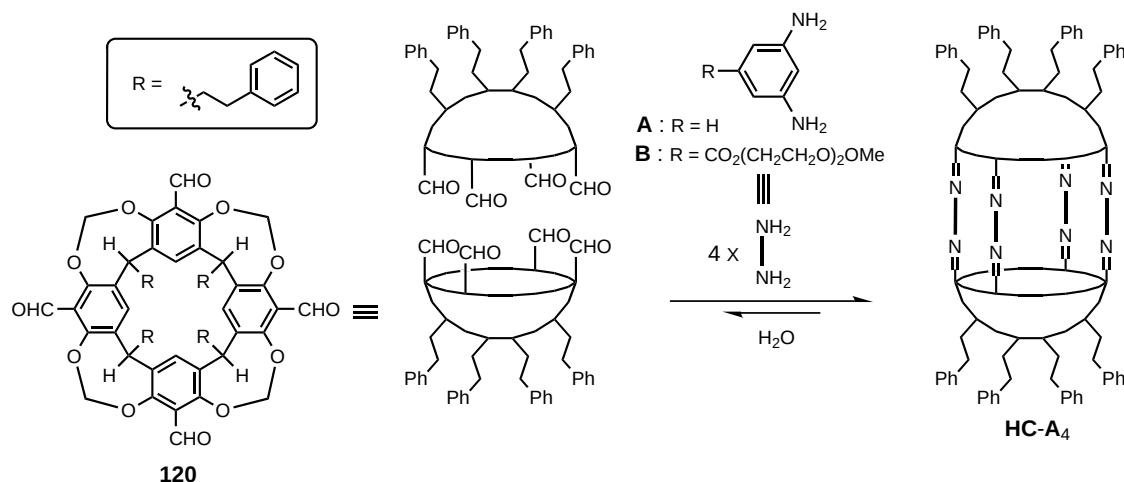
Nonetheless, dynamic covalent chemistry is beginning to make its presence felt in this area of research. In 1999, Tam-Chang et al.^[119] reported the dimerization, under equilibrium control, of the trithiol **115** to form the small cage-like macrobicyclic tris(disulfide) **116** (Scheme 47). In the presence of bis(2-hydroxyethyl)disulfide (**117**), an equilibrium is established between **115**, **116**, and the unidentified oligomeric material **118**. The addition of 2-hydroxyethanethiol (**119**) to this mixture results in the regeneration of the trithiol **115**. Whereas previous attempts^[120] to form macrocyclic bis- and tris(disulfides) were hampered by unfavorable enthalpic terms associated with strain of the C-S-S-C torsion angle, the design of this monomer allowed for the formation of relatively strain-free disulfide linkages. An investigation of the effects of guest templating upon the dynamic disulfide equilibrium would be interesting. As it stands, only 30% of the equilibrium mixture is composed of the dimeric cage **116**. It is not unreasonable to expect the equilibrium to shift to produce more of **116** upon addition of a guest that templates the formation of the macrobicyclic tris(disulfide).

The dynamic synthesis of a larger container-like molecule was subsequently reported.^[121] The addition of two equivalents of the aromatic *m*-phenylenediamine **A** to the tetraformyl cavitand **120** resulted in the near-quantitative assembly



Scheme 47. The trithiol **115** can, in the presence of **117**, form an equilibrating mixture containing macrobicyclic **116** as well as unidentified oligomeric material **118**.

of the octamine hemicarcerand **HC-A₄** (Scheme 48). Furthermore, the dynamic nature of the system was revealed upon addition of a 5-substituted *m*-phenylenediamine linker (**B**), which afforded an equilibrium mixture containing six different hemicarcerands: namely, **HC-A₄**, **HC-A₃B**, **HC-A₂B₂** (*C_{2v}* and *D_{2h}* isomers), **HC-AB₃**, and **HC-B₄**. Subsequently, the ability to open and close the hemicarcerand, by sequential hydrolysis/imine exchange and then imine formation, was exploited for the controlled release of ferrocene (Fc) from the corresponding Fc-containing hemicarceplex.^[122] The half-life for the release of Fc from Fc@**HC-B₄** in CDCl₃ was shown to be >4000 h. However, the rate of release could be altered upon the addition of 4–8 equivalents of trifluoroacetic acid



Scheme 48. Reversible formation of an imine bond between the tetraformyl cavitand **120** and small diamine linkers (here *m*-phenylenediamine^[121]) leads to the formation of octaminocarcerands.

(TFA), which reduced the half-life to about 1500 h. The addition of *m*-phenylenediamine (in addition to the acid) further accelerated the release of Fc and resulted in a half-life of 180 h. Presumably, when TFA alone catalyzes the release of Fc, traces of H₂O in the system hydrolyze one or more imine bonds, thereby opening a “door” in the hemicarceplex shell through which the Fc can escape. When *m*-phenylenediamine is present, an additional mechanism, namely imine exchange, may also be operating. Therefore, the dynamic nature of this system can be utilized to control the measured release of an incarcerated molecule from within a hemicarceplex, without destroying irreversibly the covalent shell that acts as the prison walls.

3.4. Interlocked Molecular Compounds

Interlocked molecules^[123] consist of two or more components that are linked mechanically together. Two of the simplest examples of such compounds are depicted schematically in Figure 17. A [2]catenane^[124] is comprised of two mutually interlocking rings which can only be separated upon

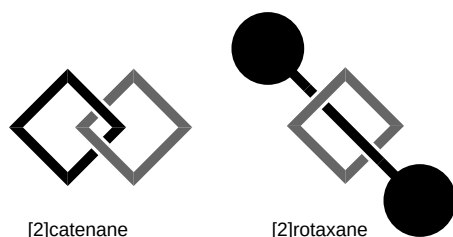
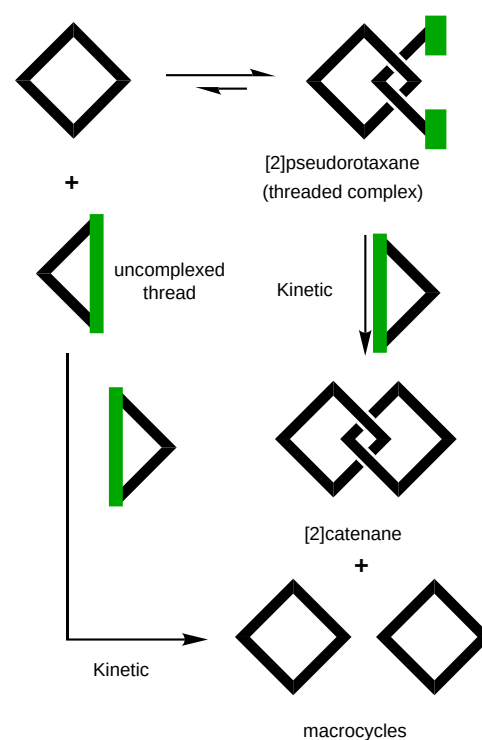


Figure 17. Schematic representations of a [2]catenane and a [2]rotaxane.

cleavage of one (or more) of the covalent bonds that constitute each macrocycle. A [2]rotaxane^[125] consists of a dumbbell-shaped component around which a ring-shaped component is trapped as a consequence of the bulky nature of the ends (or stoppers) of the dumbbell component. Once again, the components are not free to separate from one another unless a covalent bond is broken in either the dumbbell or the ring components. Although initially considered esoteric, these interlocked molecular compounds are now becoming established in the areas of molecular machinery^[126] and molecular computing.^[127]

The synthetic methodology for the construction of interlocked molecules has evolved in a remarkable fashion since the first report^[124a] of a [2]catenane appeared in 1960. To date, however, a common feature^[123–125] of the vast majority of catenane and rotaxane syntheses is the kinetically controlled final post-assembly modification step. Consequently, these strategies often result (Schemes 49 and 50) in the irreversible formation of undesired, non-interlocked, by-products, thereby reducing the overall efficiencies of these processes. For example, during the formation (Scheme 49) of a [2]catenane from a [2]pseudorotaxane^[128] by a clipping^[129] process, the competitive reaction of the uncomplexed thread (rod) will result in the formation of free macrocycle. Therefore, the isolation of both component macrocycles, in addition to the desired [2]catenane, is expected in a stoichiometric reaction.

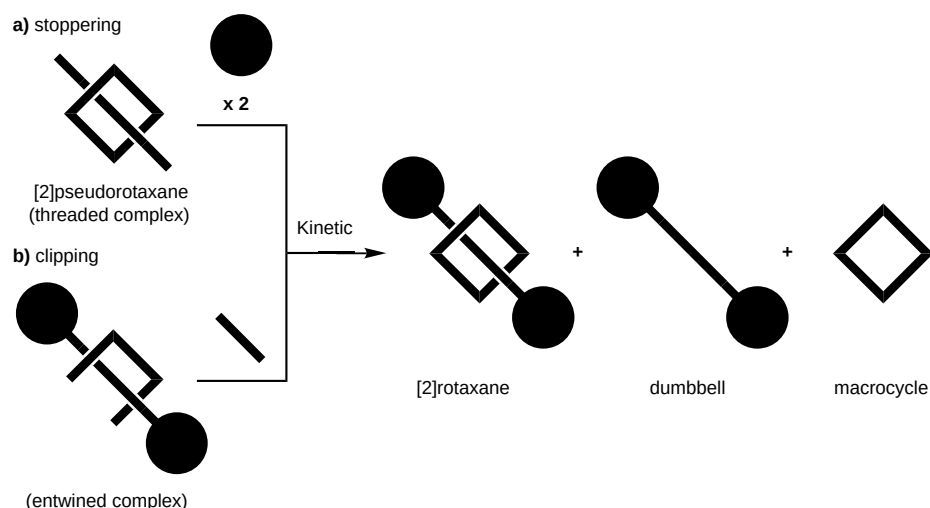


Scheme 49. A schematic representation depicting the kinetically controlled synthesis of a [2]catenane from the corresponding [2]pseudorotaxane by a clipping process. The formation of free macrocycle results from the competitive reaction in which uncomplexed threadlike molecules take part in the macrocyclization process.^[129]

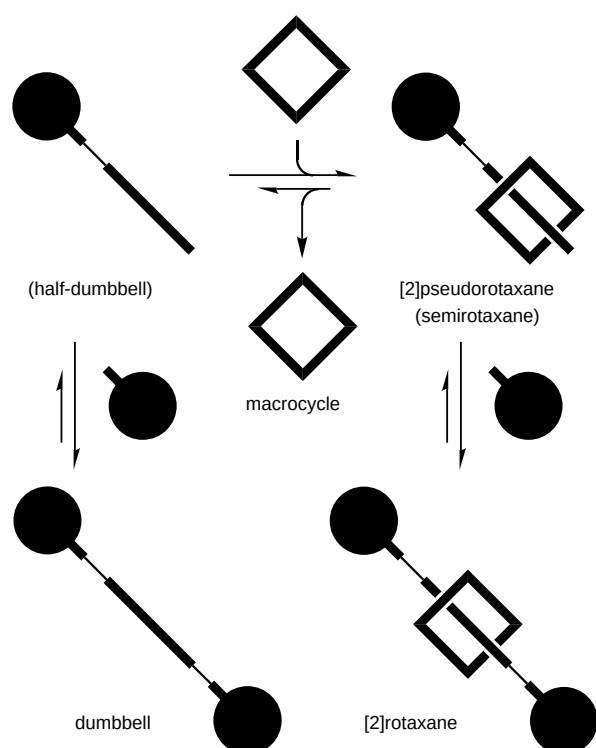
Furthermore, during rotaxane-forming reactions (Scheme 50), in which the post-assembly modification of either a threaded complex ([2]pseudorotaxane) or an entwined complex is achieved by stoppering (a) or clipping processes (b),^[129] respectively, the competitive reactions of the free rod component will give the free dumbbell and the free macrocycle.

In contrast with these kinetically controlled processes, however, a reversible thermodynamically controlled approach allows for “proof-reading” steps in which “incorrect” structures are consumed and their component parts recycled back into the equilibrating mixture. For example, in a stoppering^[129] process employing reversible covalent bond formation (Scheme 51), the free dumbbell does not represent a dead-end structure as it would if the reaction was performed under kinetic control. When a thermodynamically controlled regime operates, such an undesired product can simply undergo re-equilibration with the ring component to form the desired [2]rotaxane.^[80] Furthermore, in addition to reversible stoppering processes, the thermodynamically controlled synthesis of [2]rotaxanes using a clipping approach (wherein a macrocyclic component is clipped around a preformed dumbbell-shaped molecule) can also be envisaged (Scheme 52).

In fact, there are several ways by which dynamic [2]catenanes and [2]rotaxanes can be assembled. Different strategies can be anticipated, depending upon whether just one or both of the components possess, within their constitutions, bonds that can be made and broken reversibly (for example, **I–V** in



Scheme 50. Both stoppering (a) and clipping (b) approaches can be utilized^[129] for the synthesis of a [2]rotaxane performed under kinetic control.

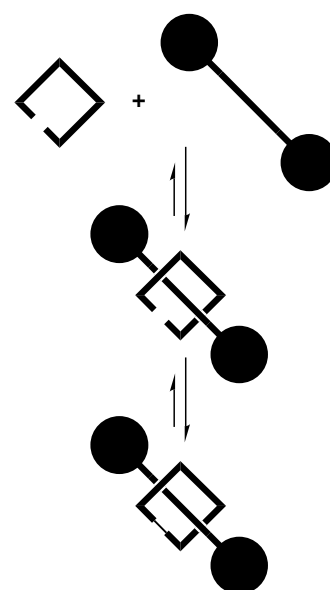


Scheme 51. A schematic representation depicting the thermodynamically controlled synthesis of a [2]rotaxane using the stoppering methodology. The thinner lines represent the reversibly formed covalent bonds; a convention that will be used in the remaining representations.

Figure 18). Additionally, the possibility exists for interlocked molecules to be constructed directly from their constituent components (Scheme 53). For example, in a process reminiscent of the conjurer's "magic rings" trick (wherein two apparently "closed" rings can be linked together, one through the other, to form a macroscopic "[2]catenane"), the mixing of two preformed macrocycles—at least one of which contains a dynamic covalent bond—can result, under the appropriate conditions, in the thermodynamically controlled synthesis of a dynamic [2]catenane. By analogy, the corresponding process

for a [2]rotaxane has been referred to as the "magic rods" trick.^[130]

Before proceeding, it is perhaps prudent to comment upon the thermodynamically controlled synthesis of "rotaxanes" (we use quotation marks because they are more accurately described as rotaxane-like "complexes") in a manner that does not require the presence of dynamic covalent bonds—namely the so-called slippage approach.^[131] The slippage approach is, at least initially, very similar to that of stoppering in that each protocol demands the



Scheme 52. A schematic representation depicting the thermodynamically controlled synthesis of a dynamic [2]rotaxane utilizing clipping methodology.

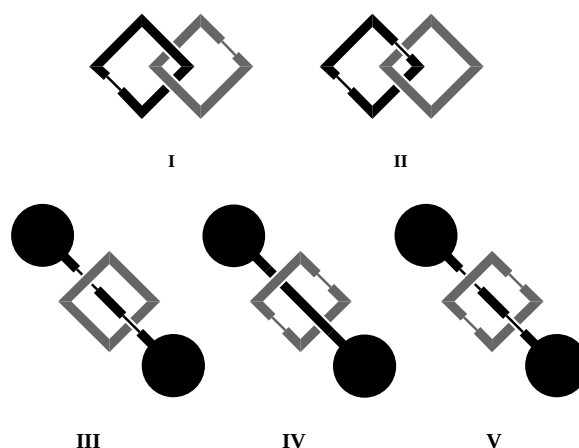
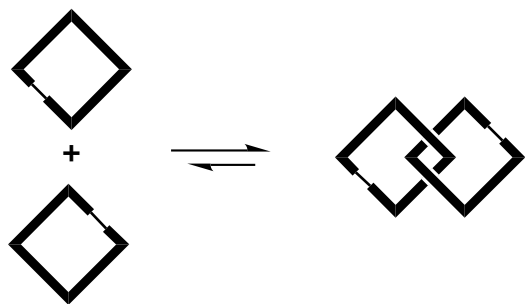
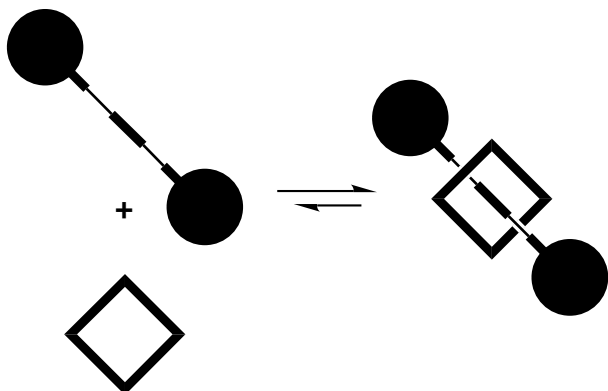


Figure 18. Some selected examples of dynamic [2]catenanes (I and II) and dynamic [2]rotaxanes (III–V). The thin lines represent dynamic covalent bonds.

a) "Magic Rings"

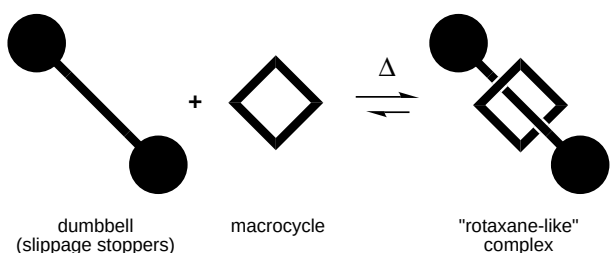


b) "Magic Rods"



Scheme 53. Schematic representations of "magic" interlocked molecules and their corresponding non-interlocked components; a) "magic rings" and b) "magic rods".

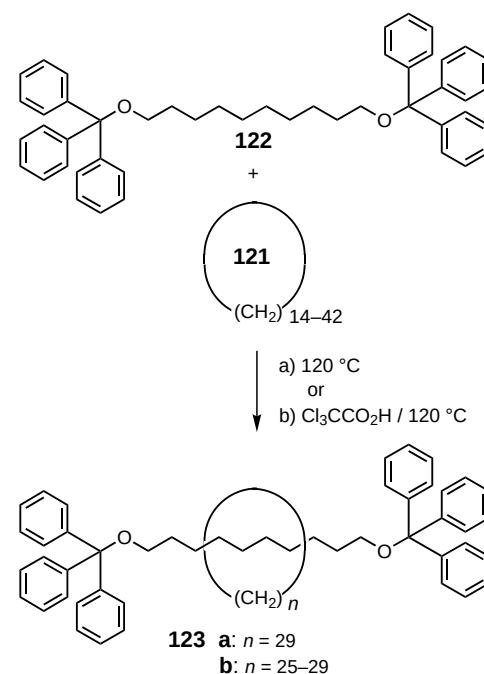
threading of a linear component through the cavity of a macrocyclic one. Subsequently, however, whereas stoppering requires bond formation to create a kinetically stable compound (a rotaxane), slippage relies upon subtle manipulation of the complexation and decomplexation rates to confer kinetic stability upon its products (rotaxane-like "complexes"). The size of the linear component's end groups relative to the dimensions of the macrocycle's aperture influences the rates at which a rotaxane-like complex is assembled/disassembled. Therefore, the judicious choice^[132] of a slippage "stopper", complementary to an appropriately sized macrocycle (Scheme 54), can result in a situation where the kinetics of threading/dethreading vary significantly over an easily accessible temperature range. The extent of this kinetic disparity can be utilized^[133] to thread a ring component onto a dumbbell capped with a slippage stopper at one



Scheme 54. The slippage^[131] synthesis of a "rotaxane-like" complex relies upon the precise matching of the end groups of the dumbbell and the size of the cavity of the macrocycle through which the dumbbell has to pass.

temperature, but essentially prevent its passage (as a consequence of extraordinarily slow kinetics) at another, lower, temperature. Hence, heating up a solution containing two such kindred components permits the thermodynamic equilibrium to be reached, which, if in favor of rotaxane-like "complex" formation, will result in a kinetically stable rotaxane-like complex upon subsequent cooling down of the solution. However, the utility of this approach is tempered by the fact that the products^[134] are stable only under certain environmental conditions; an increase in temperature, solvent polarity, and/or acidity all having profound, often deleterious, consequences upon the stabilities of the "complexes".

To the best of our knowledge at least, the first reported use of dynamic covalent chemistry being utilized for the formation of an interlocked molecule was in 1972 by Harrison.^[133a] By employing a statistical approach (relying upon the chance threading of a linear component through the cavity of a cyclic one) he heated a mixture (Scheme 55a) containing cyclic



Scheme 55. The thermodynamically controlled statistical synthesis^[133a] of [2]rotaxanes comprised of rings **121** and rods **122** using slippage (a), and threading-followed-by-stoppering (b) approaches.

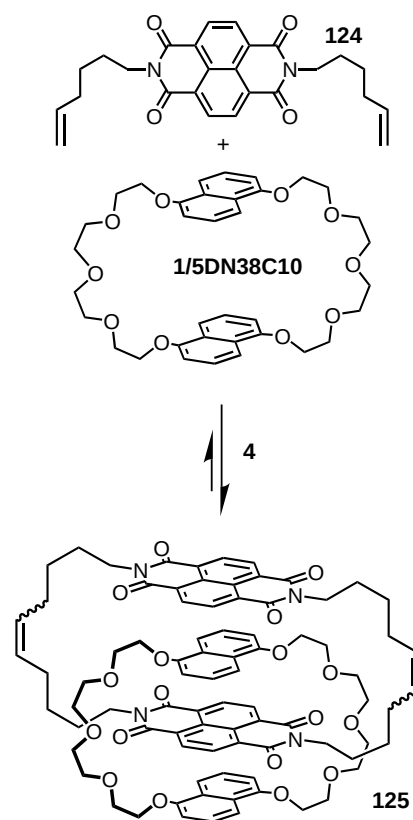
hydrocarbons **121** (ring sizes C_{14} – C_{42}) and the dumbbell-shaped compound 1,10-bis(triphenylmethoxy)decane (**122**) up to 120 °C. The [2]rotaxane **123a** comprised of the C_{29} macrocycle and the dumbbell-shaped component could be isolated chromatographically upon cooling the reaction mixture down to room temperature. At room temperature, the C_{29} macrocycle cannot pass over the bulky triaryl end groups. At 120 °C, however, the macrocycle has sufficient energy to stretch out and pass over the end groups, thus allowing the formation of a threaded, interlocked structure. Therefore, an equilibrium is established in which the threaded structure is a significant enough entity, such that a kinetically stable [2]rotaxane **123a** can be isolated upon cooling down to

room temperature (at which the macrocycle no longer has enough energy to pass over the bulky end groups).

Two other important realizations emerge from this experiment. Presumably, macrocyclic hydrocarbons of C_{30} and greater are free to pass over the triaryl end groups, even at room temperature, and hence the threaded structures containing these rings are simply pseudorotaxanes at room temperature and dissociate into their component parts when chromatographic purification is attempted. More importantly, however, as no rotaxanes containing C_{28} macrocycles and smaller are isolated, it is also possible to say that, at least for temperatures up to 120°C , macrocycles C_{28} and smaller cannot pass over the triaryl end groups.

Harrison then carried out a second experiment with the same components at the same temperature, catalyzed by the addition of small quantities of trichloroacetic acid (Scheme 55 b). In this case, once the reaction had been cooled down to ambient temperature and subjected to chromatography, a mixture of [2]rotaxanes **123b** was isolated in which the size of the macrocyclic component ranged from C_{25} – C_{29} . In confirmation of this observation, acid hydrolysis of the rotaxane mixture afforded the five macrocycles from cyclopentacosane (C_{25}) to cyclononacosane (C_{29}). Therefore, Harrison postulated that the formation of [2]rotaxanes containing rings that have already been proven to be too small (that is, $n = 25$ – 28) to “slip” over the end groups onto the decane chain must occur by a mechanism in which one, at least, of the triphenylmethyl groups of the dumbbell is reversibly cleaved (under acid catalysis) and the species that actually threads through these smaller macrocycles is the monotriphenylmethyl ether (most likely, of decane-1,10-diol) prior to reformation of the ether linkage. Except for a very similar study employing thioethers in the place of ethers by Schill et al. in 1986,^[133c] reversible covalent bond formation was not used for the synthesis of interlocked molecular compounds until the last few years of the 20th century.

It was only in 1998, that Sanders and co-workers reported the first attempt^[135] to use dynamic covalent chemistry for the thermodynamically controlled synthesis of a wholly organic [2]catenane.^[136] By utilizing a system based upon the mutual molecular recognition expressed between π -electron-rich aromatic diethers and π -electron-poor aromatic diimides,^[137] Sanders investigated the application of olefin metathesis, performed reversibly,^[138] for the thermodynamically controlled synthesis of [2]catenanes.^[139] Treatment of a CH_2Cl_2 solution containing 1,5-dinaphtho[38]crown-10 (**1/5DN38C10**) and the naphthalene-based diolefin **124** with the Grubbs’ metathesis catalyst **4** resulted in the formation of an isomeric mixture of [2]catenanes **125** (Scheme 56), which could be converted quantitatively into a single compound following catalytic hydrogenation (Pd/C) of the mixture of isomeric alkenes.^[135] Furthermore, when the ring-closing metathesis was performed on **124** without any crown ether present, a white precipitate (presumably a mixture of oligomeric species) was obtained. Upon treatment with **1/5DN38C10** this product re-equilibrated to afford the same distribution of products that were observed in the previous experiment where the crown ether was present from the outset. The results of these two experiments (different order

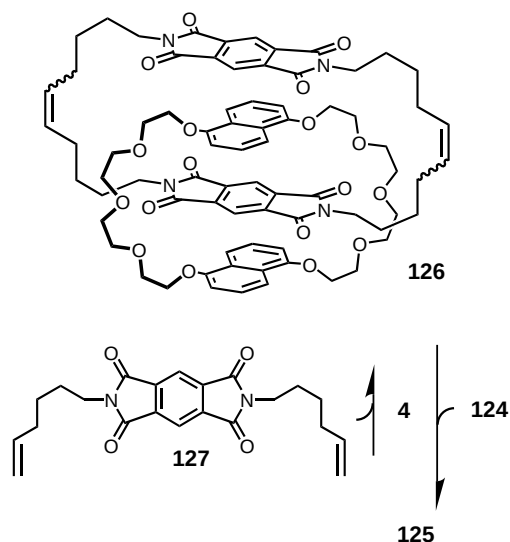


Scheme 56. Formation of a π -electron-poor/ π -electron-rich stacked [2]catenane **125** using ring-closing metathesis (RCM).

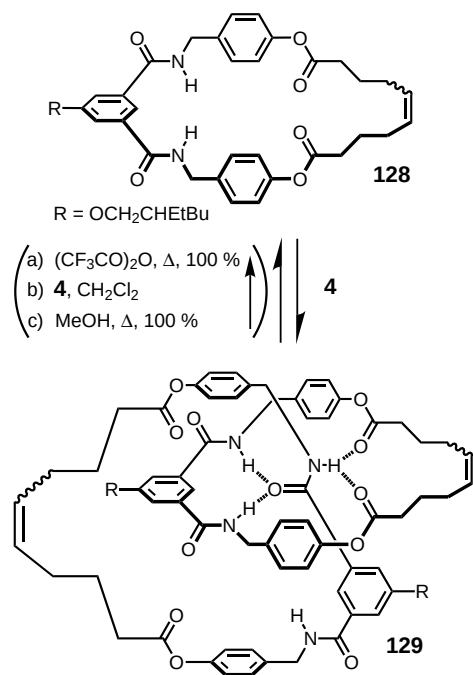
of addition but same observed product distributions) imply that the olefin metathesis reaction is indeed reversible under these conditions, and that the system is hunting for the most thermodynamically favorable products.

In an attempt to substantiate this hypothesis, an exchange experiment was performed where a diolefin-[2]catenane **126** incorporating benzene diimide groups as part of the π -electron-poor circuit was exposed to **124** in the presence of the Grubbs’ catalyst **4** (Scheme 57). The formation of the thermodynamically more stable [2]catenane **125** was anticipated from the stronger interaction observed between naphthalene bis(carboximides) with **1/5DN38C10** than that involving benzene bis(carboximides).^[137a] Although this product was indeed observed to form, protracted reaction times were necessary, and the slow reaction kinetics ultimately prevented the system from reaching equilibrium. Despite these difficulties, however, the principle of reversibility in the synthesis of wholly organic catenanes had been demonstrated, as well as showing that olefin metathesis was a viable choice for the formation of a dynamic covalent bond.

Olefin metathesis was also utilized by Leigh and co-workers^[140] in their synthesis of “magic rings” in the form of a wholly organic [2]catenane. Under the appropriate conditions, treatment of a benzylic amide macrocycle **128** containing an internal olefin unit with the Grubbs’ catalyst **4** resulted in the self-assembly of the corresponding [2]catenane **129** (Scheme 58). Furthermore, the distribution of products (that is, the amount of macrocycle versus catenane) obtained at equilibrium was shown to depend markedly upon the



Scheme 57. Reversible metathesis reactions can be employed^[135] to exchange the π -electron-poor benzenebis(carboximide) components of dynamic [2]catenanes for more thermodynamically favored naphthalene-bis(carboximide) building blocks.



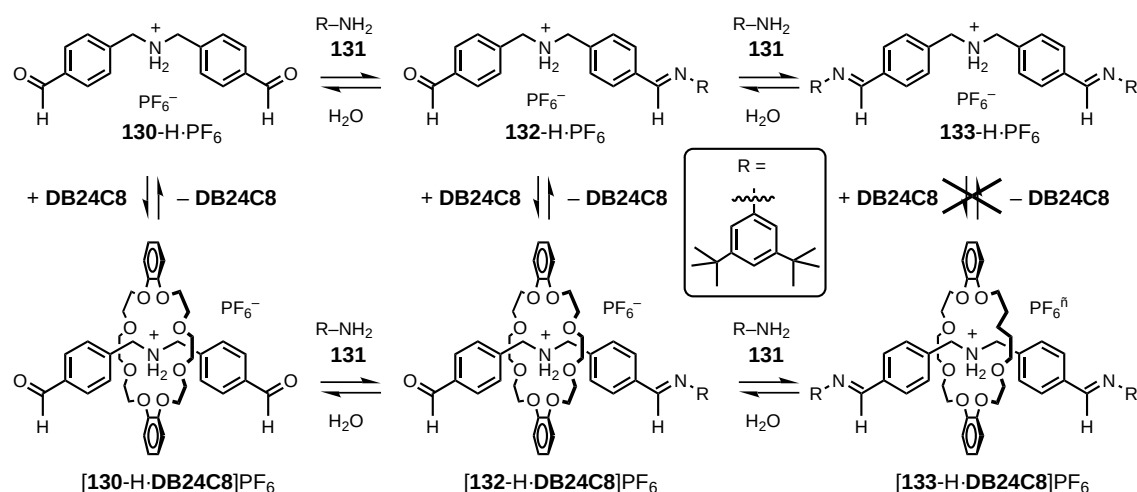
Scheme 58. Reversible olefin metathesis is employed^[140] for the synthesis of [2]catenanes under thermodynamic control. Their complete disassembly is achieved upon protection of the amide groups, followed by treatment with **4**, and subsequent deprotection.

concentration of macrocycle employed initially in the reaction. Only the free macrocycle could be detected in the equilibrium mixtures at very low concentrations (≤ 0.2 mM). In contrast, however, when the reaction was performed using a macrocycle concentration of 200 mM, $>95\%$ of the resulting equilibrium mixture consisted of a mixture of the three isomeric diolefin [2]catenanes (*EE*, *EZ*, and *ZZ*). At concentrations in between these two extremes, significant amounts of both the free macrocycle and isomeric [2]catenanes co-exist at equilibrium. Crucially, when the mixture of products obtained

at any one given concentration was re-exposed to the metathesis catalyst at another concentration, the product distribution was observed to shift to the one that would have been obtained if only the macrocycle (or indeed [2]catenane) had been metathesized itself, which demonstrates that the system is operating under thermodynamic control. Here again, reduction (Pd/C) of isomeric mixtures of interlocked molecules afforded quantitatively, kinetically stable saturated analogues.

Leigh and co-workers^[140] then went on to demonstrate how the controlled disassembly (Scheme 58) of the catenane **129** could be achieved by a series of simple chemical transformations. Trifluoroacetylation of the amide groups in the dynamic [2]catenane, followed by exposure to the Grubbs catalyst, resulted in the formation of the free macrocycle—independent of the concentration at which the reaction was performed—as the capacity for hydrogen bonding^[141] to occur between two (pre)macrocyclic components had been negated upon protection of the amide groups. Subsequently, removal of the metathesis catalyst, followed by cleavage of the trifluoroacetyl groups in refluxing MeOH, afforded the original benzylic amide macrocycle **128**. Therefore, by utilizing amide hydrogen bond recognition, in conjunction with reversible olefin metathesis, the thermodynamically controlled self-assembly of [2]catenanes by a “magic rings” strategy had been demonstrated successfully for the first time.

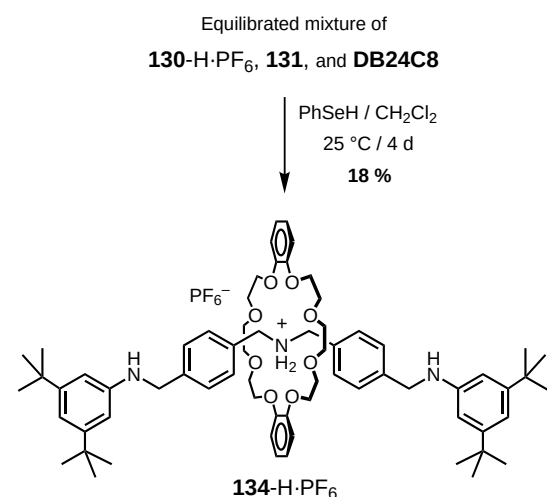
Apart from the initial forays by Harrison et al. and Schill et al., the thermodynamically controlled synthesis of wholly organic rotaxanes was largely unexplored until the utility of the imine bond^[142] to act as the reversible linker in the formation of dynamic interlocked molecular structures was investigated. By utilizing the well-established^[125b, 143] secondary ammonium ion/crown ether recognition motif, we designed a system^[144] in which the thermodynamically controlled self-assembly of a [2]rotaxane could be achieved by exploiting the reversible formation of the imine bond. Treatment of the bis(4-formylbenzyl)ammonium salt **130-H**·PF₆ with two equivalents of 3,5-di-*tert*-butylaniline (**131**) resulted in an equilibrium mixture which contained a small amount of dialdehyde **130-H**·PF₆ (4%), some mono-imine **132-H**·PF₆ (23%), and mainly the diimine dumbbell-shaped compound **133-H**·PF₆ (73%; Scheme 59, top). If the system was not dynamic, addition of one equivalent of **DB24C8** to this mixture should result in no more than $4 + 23 = 27\%$ of the rotaxane species. The remaining 73% of the NH₂⁺ centers in the middle of the diimine dumbbell are inaccessible, as **DB24C8** cannot pass over the 3,5-di-*tert*-butylphenyl groups. However, following addition of the crown ether (Scheme 59, bottom), the species present in the equilibrium mixture (established after about 5 days) had 77% of their NH₂⁺ centers encircled by **DB24C8** macrocycles—the major species present (47%) in solution was the diimine [2]rotaxane [**133-H**·**DB24C8**]PF₆, the other occupied centers being in the [2]semirotaxane [**132-H**·**DB24C8**]PF₆ (26%) and the [2]pseudorotaxane [**130-H**·**DB24C8**]PF₆ (4%). Furthermore, the same equilibrium proportions of these species were reached much more quickly (1.5 days) when **DB24C8** was added to the dialdehyde salt **130-H**·PF₆ prior to addition of the aniline **131**. Therefore, the fact that the same equilibrium



Scheme 59. The dynamic equilibrium that is established^[144] upon dissolution of **130-H**·PF₆, **131**, and **DB24C8** (1:2:1) in CD₃CN.

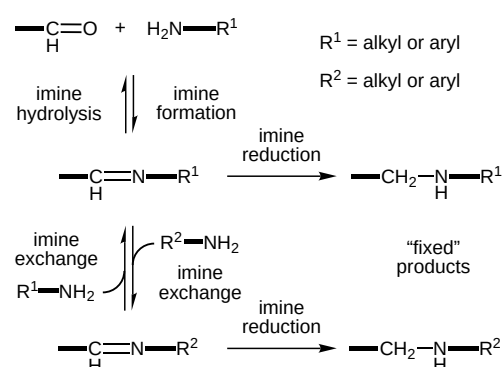
composition is attained irrespective of the order of addition of the individual components suggests that the system is operating under thermodynamic control.

Of course, kinetic “fixing” of an equilibrating system is usually necessary to facilitate the isolation of discrete, characterizable products. With imines, this outcome can be achieved upon reduction of the carbon–nitrogen double bond to the corresponding single bond, thus rendering it a static, rather than a dynamic, amine linkage. Treatment of the equilibrating mixture, obtained upon mixing **130-H**·PF₆, **131**, and **DB24C8**, with benzeneselenol^[145] led to the “fixed” diamine [2]rotaxane **134-H**·PF₆ being isolated in 18% yield (Scheme 60).



Scheme 60. “Fixing” of the dynamic system upon reduction with PhSeH.^[144]

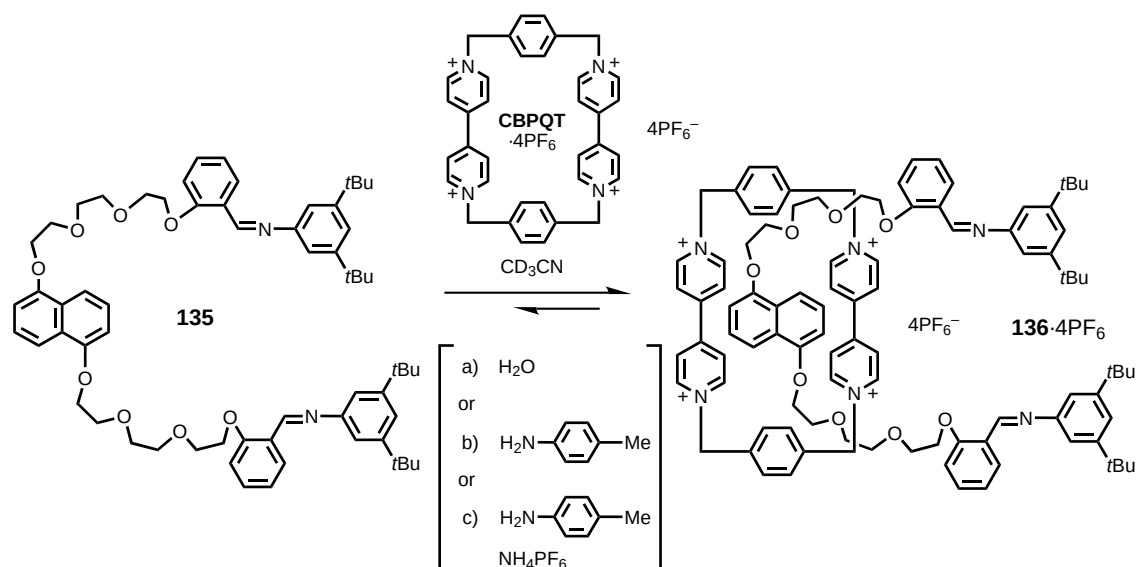
The utility of the imine bond lies, not only in its reversible formation/hydrolysis, but also in its capacity to undergo exchange reactions with other amines to form new imines (Scheme 61). This property was exploited by Rowan and Stoddart^[146] for the dynamic synthesis of [2]rotaxanes based upon the π -electron-rich/ π -electron-poor recognition expressed between diaryl ethers and bipyridinium cations.^[147]



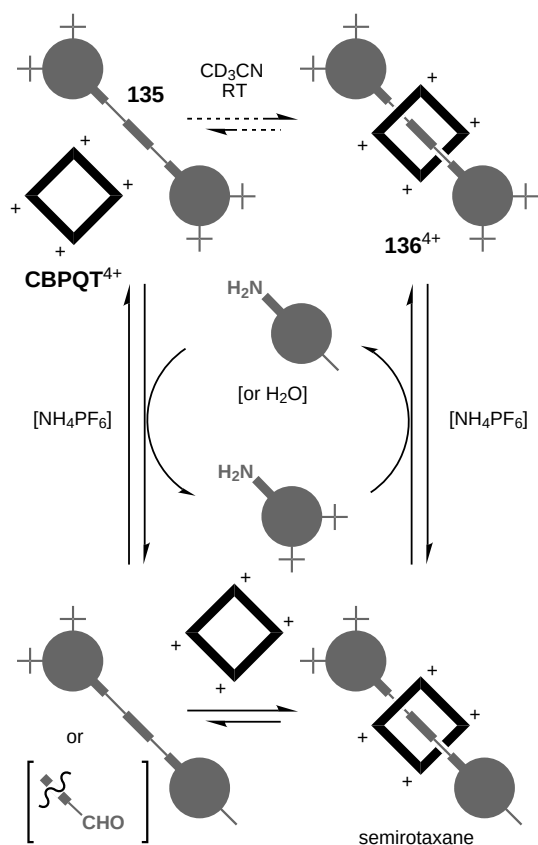
Scheme 61. Some important reactions of imines.

When mixed with the naphthalene-containing diimine dumbbell **135**, the tetracationic cyclophane^[148] **CBPQT**·4PF₆ slowly finds its way onto the 1,5-dioxynaphthalene recognition site over a period of two weeks to form the corresponding [2]rotaxane **136**·4PF₆ (Scheme 62a). As the **CBPQT**·4PF₆ cyclophane cannot pass over the bulky 3,5-di-*tert*-butylphenyl stoppers of the dumbbell-shaped component, the mechanism of this process is believed to be that of imine hydrolysis caused by a small amount of water present in the sample.

However, when the experiment was repeated using a catalytic amount of 4-toluidine, equilibrium was reached inside two days, rather than taking two weeks, which suggests that the major pathway for rotaxane formation involves imine exchange (Scheme 62b). Once the smaller aniline replaces the larger one, the group that was acting as a stopper, **CBPQT**·4PF₆ is now able to pass over the smaller end group onto the π -electron-rich 1,5-dioxynaphthalene recognition site (Scheme 63). Subsequent re-exchange of the imine, in which the 4-methylphenyl group is swapped back for the original 3,5-di-*tert*-butylphenyl group, traps the tetracationic cyclophane on the dumbbell-shaped component and so completes the exchange cycle. Furthermore, when the “magic rod” experiment was performed in the presence of a catalytic amount of weak acid (NH₄PF₆), in addition to the 4-toluidine,



Scheme 62. The diimine dumbbell **135** and the tetracationic cyclophane **CBPQT**·4PF₆ form the dynamic [2]rotaxane **136**·4PF₆ when mixed together in the presence of a) H₂O, b) *p*-toluidine, and c) *p*-toluidine:NH₄PF₆.^[146]



Scheme 63. A schematic representation depicting the proposed mechanism by which the tetracationic cyclophane **CBPQT**⁴⁺ threads onto the diimine dumbbell-shaped compound **135**.

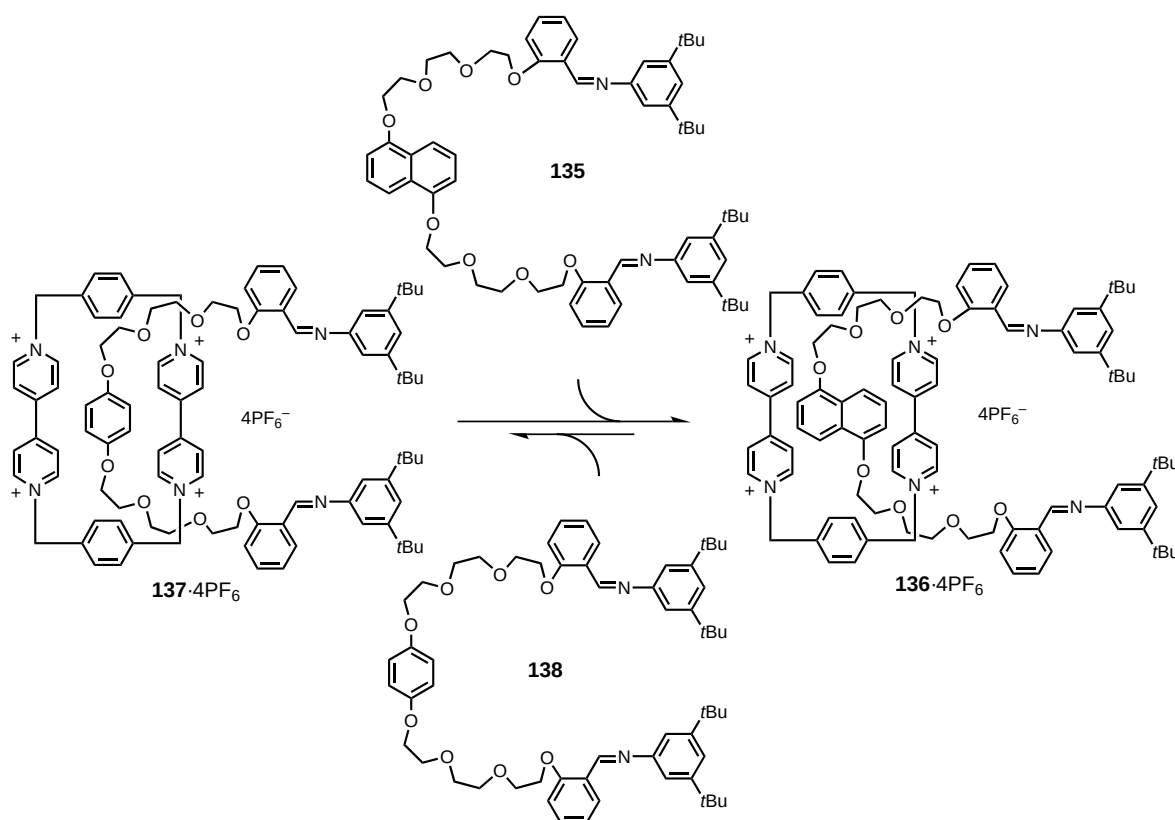
equilibrium was reached in under 2 h (Scheme 62c), thus confirming the expected rate enhancement for imine exchange under mildly acidic conditions.

A dumbbell exchange experiment was performed to highlight the thermodynamic nature of this system. Treatment of

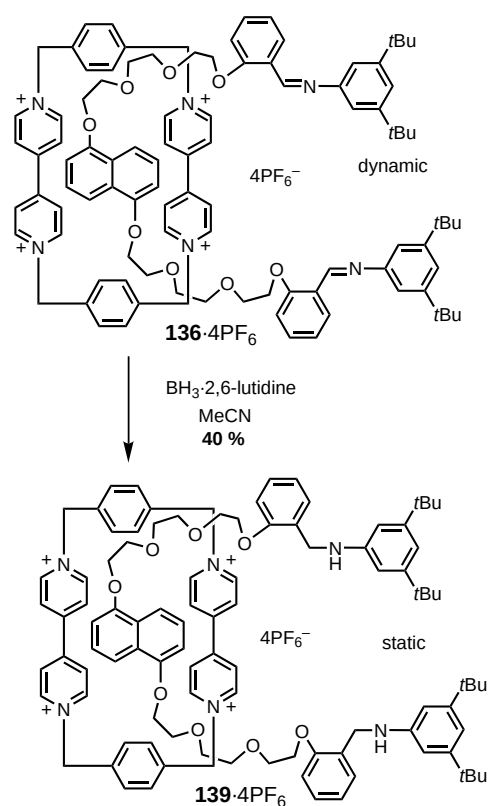
the dynamic diimine [2]rotaxane **137**·4PF₆ (containing a 1,4-dioxybenzene-based dumbbell) with the 1,5-dioxynaphthalene-containing dumbbell **135** in the presence of both 4-toluidine and NH₄PF₆ resulted in an equilibrium mixture containing six times as much of the [2]rotaxane containing the 1,5-dioxynaphthalene-based dumbbell than the corresponding 1,4-dioxybenzene-derived one (Scheme 64). This equilibrium ratio of [2]rotaxanes reflects the stronger binding affinities^[148b, 149] of naphthalene-based derivatives, compared with benzene-based ones with **CBPQT**·4PF₆.

Finally, the ability to trap the imine systems kinetically upon reduction to the corresponding amines was also investigated. In this case, the reductant of choice was BH₃·2,6-lutidine, which was used to convert (Scheme 65) the dynamic [2]rotaxane **136**·4PF₆ into the corresponding fixed diamine [2]rotaxane **139**·4PF₆ in 40 % yield.

A common feature of the thermodynamically controlled syntheses of [2]rotaxanes discussed so far is the fact that the reversible covalent linkage has been located in the dumbbell component, thus requiring the syntheses to proceed by a threading-followed-by-stoppering strategy.^[150] Recently, however, Stoddart and co-workers reported^[151] the thermodynamically controlled synthesis (Scheme 66) of a dialkylammonium ion based [2]rotaxane in which a crown ether like macrocycle **142** is clipped^[152] around a dumbbell-shaped component. When 2,6-pyridinedicarboxaldehyde (**140**) is treated with diamine **141**, an equilibrium mixture, which appears to be comprised of many different cyclic and acyclic oligomeric species, is obtained after 24 h. However, addition of bis(3,5-dimethoxybenzyl)ammonium hexafluorophosphate (**143**·H·PF₆) to this equilibrium mixture has a dramatic effect. After only 4 mins, a new equilibrium state is reached, in which the main component is the [2]rotaxane **144**·H·PF₆. This result suggests that the dibenzylammonium ion templates the formation of the crown ether like macrocycle around itself, thus generating the interlocked molecule. The imine bonds of this [2]rotaxane were reduced by treatment with BH₃·2,6-

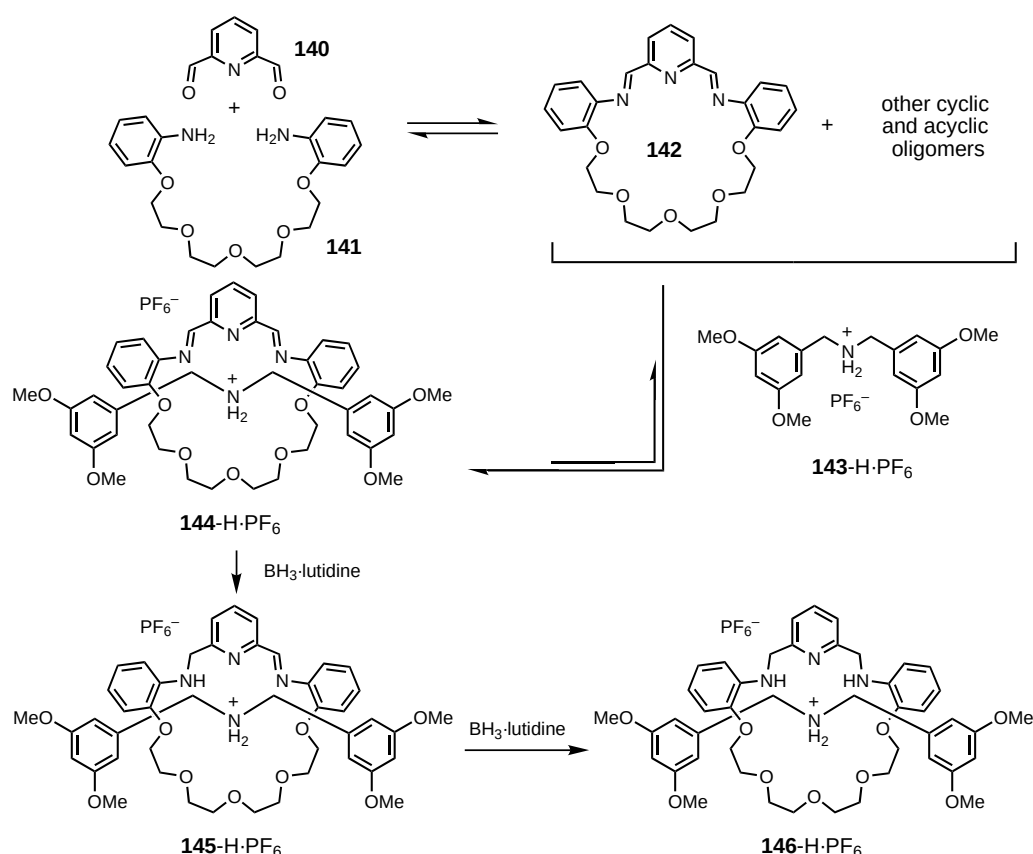


Scheme 64. Under appropriate imine exchange/hydrolysis conditions, the benzo-containing dumbbell component of the dynamic [2]rotaxane **137**·4PF₆ can be replaced by the naphthalene-containing analogue **135** to afford the more thermodynamically favored dynamic [2]rotaxane **136**·4PF₆ and the uncomplexed benzo-containing diimine dumbbell **138**.^[146]



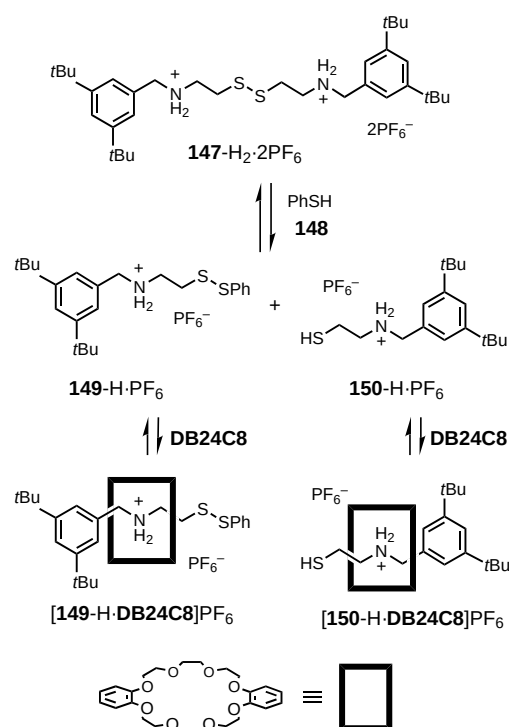
Scheme 65. Reduction of the dynamic [2]rotaxane **136**·4PF₆ affords^[146] the kinetically stable diamino-[2]rotaxane **139**·4PF₆.

lutidine complex in order to confer kinetic stability. As expected, the reduced [2]rotaxane was observed to form, but interestingly, the free dibenzylammonium ion dumbbell remaining in solution was also seen to disappear. Eventually, all of the dialkylammonium salt **143**-H·PF₆ and macrocyclic precursors are converted, via the intermediacy of **144**-H·PF₆ and the monoreduced species **145**-H·PF₆, into the kinetically stable [2]rotaxane **146**-H·PF₆ (Scheme 66). This result indicates that the reduction of imine bonds in the interlocked structures is occurring at a faster rate than those imine bonds in free macrocycles or acyclic oligomers. Therefore, as more of the kinetically stable **146**-H·PF₆ is formed, its removal from the equilibrium mixture is compensated for by the equilibrium between threaded and free macrocycles shifting to form more of **144**-H·PF₆ and **145**-H·PF₆. Although the imino groups of the interlocked structures are not as accessible sterically as those in free macrocycles or acyclic species, the presence of the NH₂⁺ center in the rotaxanes is thought to provide a mildly acidic environment for the addition of the B-H bond to these particular imines, thereby catalyzing their reduction. The whole process, namely, thermodynamic formation of the diimine [2]rotaxane followed by kinetically controlled borane reduction, is somewhat reminiscent of enzyme catalysis^[153] and also catalysis^[154] employing synthetic enzyme mimics, whereby an initial recognition process results in a substrate preorganization and hence access to a conformation which lowers the activation barrier for the final reaction.

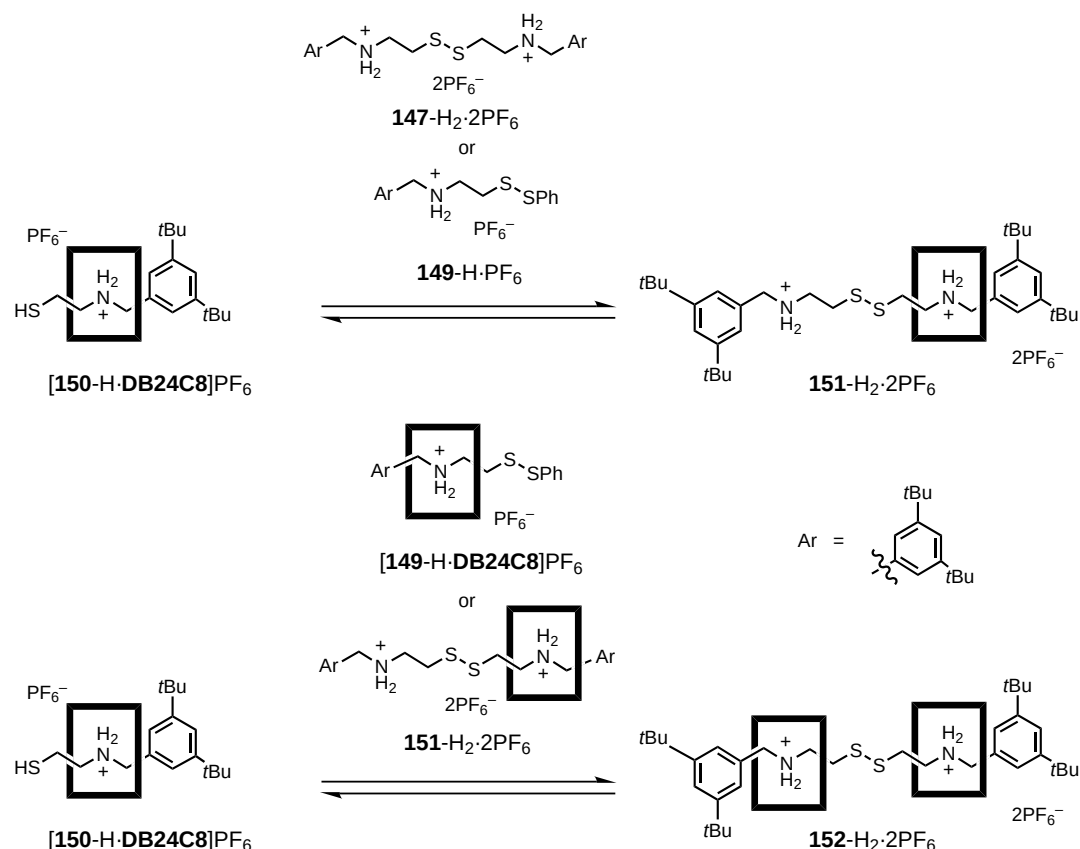


Scheme 66. The reaction of macrocycle **142** with **143-H·PF₆** leads to the equilibrium being shifted to form almost exclusively the [2]rotaxane **144-H·PF₆**. Subsequent reduction affords the kinetically stable [2]rotaxane **146-H·PF₆** in essentially quantitative yield.^[151]

Although disulfide linkages have been employed in the synthesis of both catenanes^[155] and rotaxanes,^[156] the first report^[157] of this potentially reversible bond being employed to construct an interlocked molecule under thermodynamic control appeared in early 2000. Takata and co-workers^[157] synthesized a symmetrical dumbbell-shaped compound **147-H₂·2PF₆** possessing two secondary ammonium ion centers as well as a centrally located disulfide linkage. In the knowledge that dibenzo[24]crown-8 (**DB24C8**) can bind secondary dialkylammonium ions within its macroring,^[143] two equivalents of this crown ether were added (Scheme 67) to a solution of **147-H₂·2PF₆** in CD_3CN . No crown ether was observed to thread onto the dumbbell containing the ammonium ion as the 3,5-di-*tert*-butylphenyl end groups are far too large to pass through the cavity of the **DB24C8** macrocycle, even when the solution was heated to 100 °C. However, the slow formation (equilibrium is reached after 30 days) of both [2]- and [3]rotaxanes (8 and 58%, respectively) was observed upon addition of a catalytic amount of benzenethiol **148**. The small amount of catalytic thiol acts to “unlock” the disulfide bond in the dumbbell and create two threads containing ammonium ions (**149-H·PF₆** and **150-H·PF₆**) which are both now capable of threading through a **DB24C8** macrocycle. Subsequent attack of the thiol-terminated [2]pseudorotaxane [**150·DB24C8**]PF₆ on any of the disulfides (**147-H₂·2PF₆**, **149-H·PF₆**, [**149·DB24C8**]PF₆, or **151-H₂·2PF₆**) present in solution results in the formation of either a [2]- or [3]rotaxane, **151-H₂·2PF₆** and **152-H₂·2PF₆**, respectively (Scheme 68). Takata and



Scheme 67. **147-H₂·2PF₆** reacts with thiophenol (**148**) to form^[157] two different “half-dumbbell” molecules **149-H·PF₆** and **150-H·PF₆**, which can each thread through the cavity of **DB24C8** to form the corresponding [2]semirotaxanes, [**149-H·DB24C8**]PF₆ and [**150-H·DB24C8**]PF₆, respectively.



Scheme 68. The thiol-terminated [2]semirotaxane **[150-H·DB24C8]PF₆** shown in Scheme 67 can subsequently undergo exchange reactions with other disulfide species present in solution to form **151-H₂·2PF₆** and **152-H₂·2PF₆**.^[157]

co-workers also went on^[157] to show that increases in both temperature and catalyst loading resulted in equilibrium being reached more quickly in this dynamic system. However, higher temperatures also shifted the equilibrium such that the [2]rotaxane, rather than the [3]rotaxane, became the dominant product.

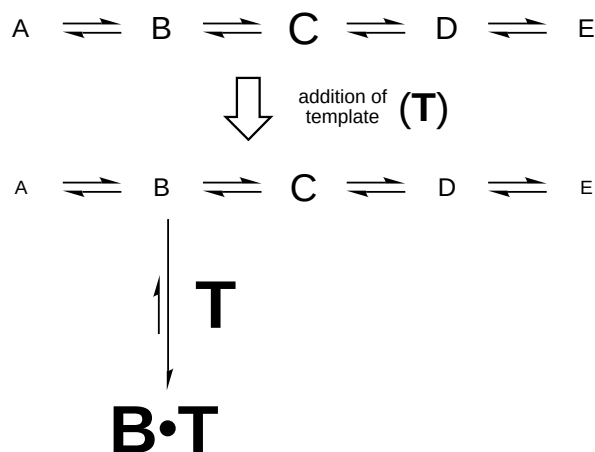
It is now clear that four of the five dynamic interlocked structures depicted schematically in Figure 18 have been examined. A dynamic [2]catenane in which each ring contains one or more reversibly formed covalent bonds (**I**) can be utilized for the self-assembly of homocircuit [2]catenanes, as demonstrated by Leigh and co-workers.^[140] However, as shown by Sanders and co-workers,^[135] a dynamic [2]catenane (**II**) can be assembled that is comprised of one static ring and one reversibly formed ring, thereby affording a heterocircuit [2]catenane. It has been shown that both structures **III** and **IV** can be utilized successfully in the self-assembly of dynamic [2]rotaxanes.^[144, 146, 151, 157] The reversibly formed component can be located in either the dumbbell (**III**) or ring (**IV**) components, thus allowing for threading-followed-by-stoppering and clipping approaches, respectively. It should be noted that structure **V**, in which both components of the [2]rotaxane contain reversibly formed linkages, is largely redundant, as the only advantage of each component in an interlocked assembly having dynamic covalent bonds arises in cases where a homocircuit [2]catenane is desired.^[140] A [2]rotaxane comprised of a dynamic ring, as well as of a dynamic dumbbell requires a certain orthogonality in the

choice of the reversible reactions chosen for each component, that is, the formation of the ring should not interfere with the formation of the dumbbell and vice versa.

In summary, the use of thermodynamically controlled approaches for the synthesis of wholly organic interlocked molecules is slowly growing in popularity. The use of olefin metathesis,^[135, 140] imine formation/exchange,^[144, 146, 151] and disulfide exchange^[157] as the reversible covalent step—in addition to the exploitation of different molecular recognition motifs^[137, 141, 143, 147]—demonstrates the generality of thermodynamically controlled approaches for the synthesis of interlocked molecules.

4. Dynamic Combinatorial Libraries

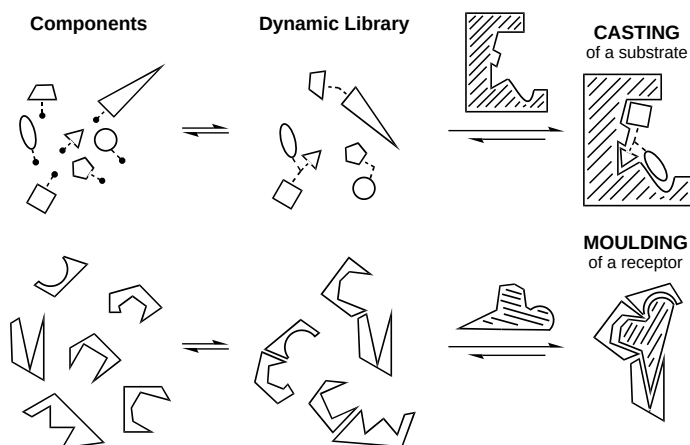
Dynamic combinatorial chemistry (DCC) exploits reversible covalent chemistry to generate combinatorial libraries that are under thermodynamic control.^[3, 158] The use of DCC has enabled combinatorial pools of candidates to be established through reversible connections, either by using covalent or noncovalent chemistry. Such a collection of molecules is termed^[159] a dynamic combinatorial library (DCL) and may be viewed as a collection of reversible assemblies of a series of building blocks which undergo thermodynamic exchange with each other (Scheme 69). Since the library members interconvert by equilibrium processes, any stabilization of a given member of the library will result in



Scheme 69. Schematic representation of the interconversion of library members by equilibrium processes. The letter sizes are representative of product concentration.

the thermodynamic redistribution of the equilibrium to yield a new thermodynamic equilibrium. The result, which is in accordance with the Le Chatelier principle, is amplification of the stabilized library member,^[80] whose formation is favored above all other possible members that might co-exist in solution. Indeed, those other possible members are “proof-read” and consumed to produce more of the favored member.

Stabilization of a library member may be achieved by introducing a template into the DCL. Templating of DCLs has been divided by Huc and Lehn^[160] into two classes (Scheme 70): “casting” and “moulding”. Casting refers to a



Scheme 70. Diagrammatic representation of casting and moulding in DCLs. In casting, a macromolecule provides a cavity within which the optimum ligand may be trapped, whereas, in moulding, the ligand collects the optimum receptor around itself.

template effect that the cavity of an enzyme, protein, or other macromolecule may have on a DCL, and molding refers to processes in which macrocyclic or macromolecular structures assemble around a template molecule. Both of these processes are driven by binding energies associated with molecular recognition and thus a DCL may evolve to form the most favored host or guest for the added template. The nature of the template used defines the molecular functions that the

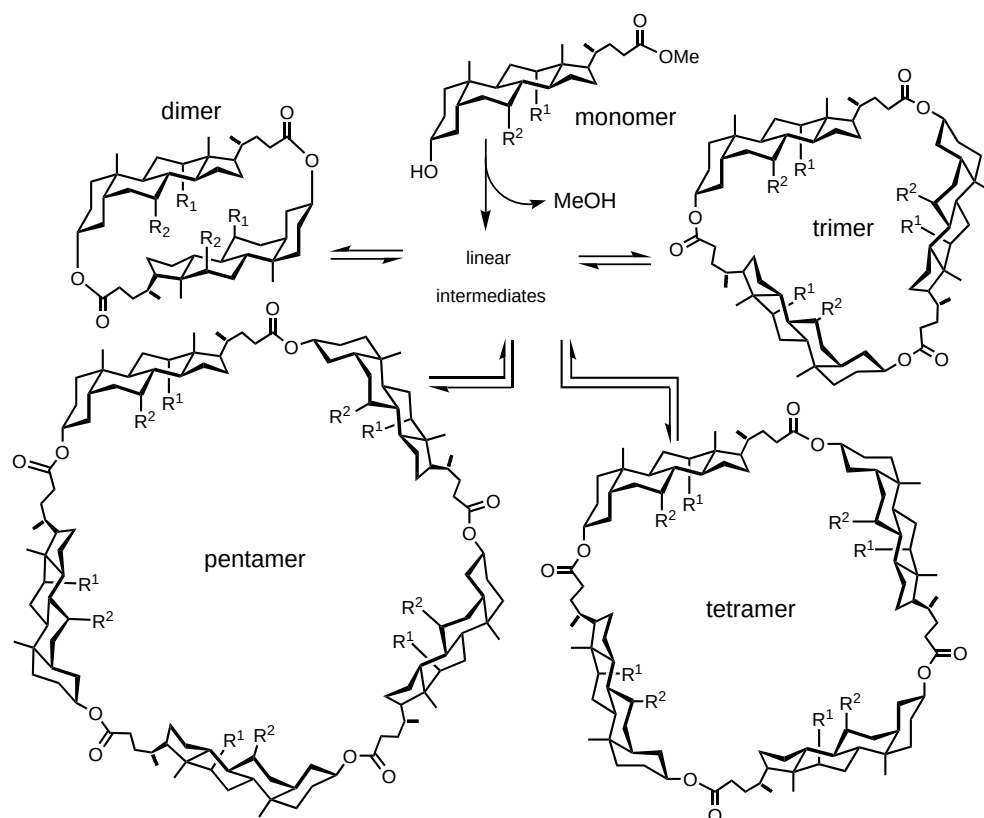
identified hosts or guests express. For example, if the template chosen is a transition state analogue for a given reaction, it can be expected that a receptor for the template will catalyze the reaction.^[158, 161] On the other hand, hosts identified by employing casting processes may be enzyme inhibitors, drug molecules, or supramolecular sensors. The reversible self-assembly of drug molecules is not a new concept and has been explored by Rideout and co-workers;^[162] their work, however, had no combinatorial dimension to it.

The inherent advantage of DCLs over their “static” counterparts is that all of the library members need not be explicitly identified, since the template provides information directly about its preferred host or guest. Thermodynamic control and proof-reading may reduce a library of say 1000 compounds to a handful of lead compounds that bind well to the template. This process is akin to template-assisted molecular evolution, wherein template effects amplify good binders of the template. Consequently, all members of the DCL are screened for binding to the template, but only the successful candidates survive. They are then identified by traditional techniques, thus eliminating the challenging analytical procedures required in the analysis of static combinatorial libraries. In this manner, thermodynamic chemistry allows us to increase the chances of drug and catalyst discovery by virtue of the numbers of candidates involved, without the complications of identification and isolation of lead compounds associated with static combinatorial chemistry.

The shifting of equilibria through use of binding events has a long but fragmented history. Publications which articulated and generalized the concept began to appear in the mid-1990s; for example, Sanders and co-workers^[163] demonstrated the “living” macrolactonization of building blocks derived from cholic acid to afford interconverting cyclic oligocholates with a product distribution under thermodynamic control. The building blocks were monomers with an AB design, with both functionalities required for reversible bond formation being incorporated into the same molecule. Conceptually, macrocycles may be envisaged to possess cavities in which to effect catalysis. The cyclic products (cyclic dimer, trimer, tetramer, pentamer, and low levels of higher oligomers) interconvert (Scheme 71) by means of base-catalyzed transesterifications, but are stable robust molecules in the absence of a catalyst.

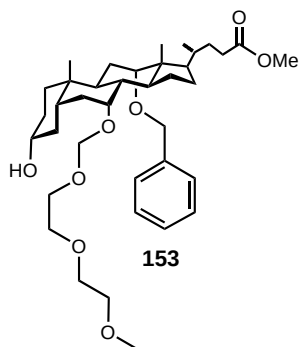
This early demonstration that a library of more than four macrocyclic species can be formed from a simple building block has been extended. The chemistry is general and a wide range of molecular scaffolds functionalized with both an alcohol and methyl ester may undergo transesterification to generate diverse DCLs of cyclic oligomers. Molecular scaffolds based on cholates and xanthene,^[112] as well as cinchona^[164] and ephedra^[165] alkaloids have been synthesized by Sanders, Rowan, and co-workers, and their resulting DCLs have been investigated. Exchange and thermodynamic equilibria have been proven for mixtures of cyclic oligomers formed in transesterification DCLs from cinchona alkaloid (Scheme 42) and cholate based monomers.^[110, 163]

Attempts have been made to influence the product distributions of libraries formed as a result of transesterifica-



Scheme 71. An equilibrating mixture of cyclic steroid oligomers exchanging through transesterification.

tions. Brady and Sanders^[159] observed that the product distribution of a DCL formed from a cholate **153** may be influenced by the introduction of alkali metal ions into the thermodynamic mixture. The general trend observed is that sodium ions favor the formation of larger macrocycles, whereas large ions, such as Cs^+ , shift the product distribution to smaller macrocycles.



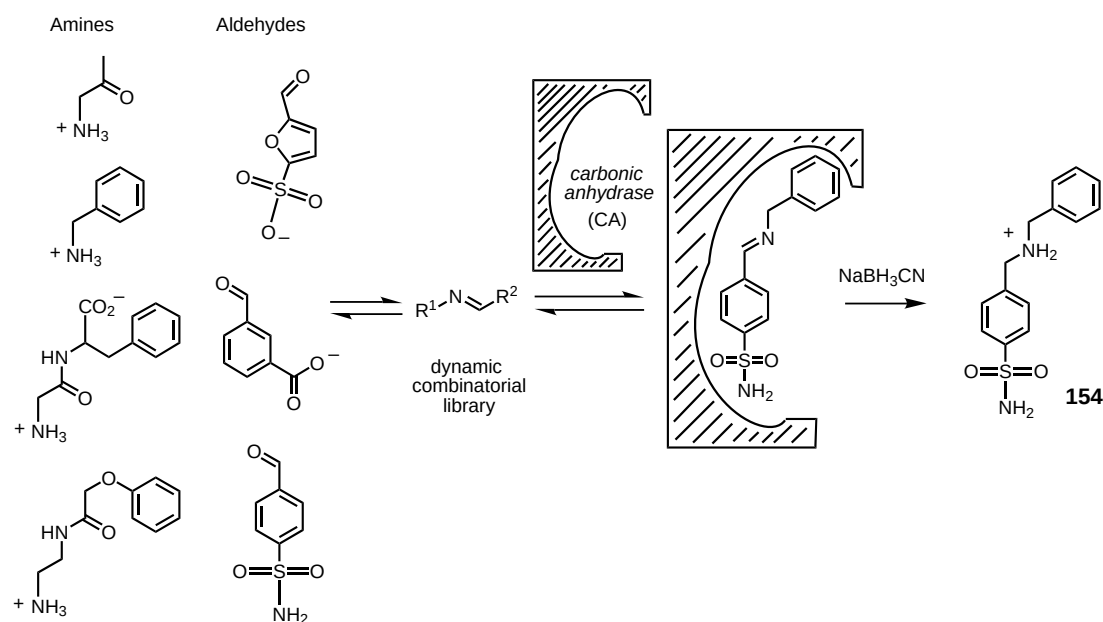
Despite proof-of-concept relating to DCL generation as a consequence of transesterification, there are limitations associated with this reaction, namely, the conditions required to effect exchange; for example, transesterification is catalyzed by potassium methoxide in the presence of [18]crown-6 in toluene under reflux. These conditions not only preclude the use of a wide range of functional groups that may have a role in template recognition but the elevated temperatures required are also highly detrimental to supramolecular interactions.

The considerations that arose with transesterification highlight a few of the many requirements^[158f] of a reversible reaction chosen for DCC. First and foremost, the rate of exchange must be such that proof-reading and editing may be performed on a suitable timescale. DCC achieves very little if thermodynamic equilibrium is not attained over a period of

weeks to months. It follows that it must be possible to “switch off” exchange, otherwise removal of the template will simply reinstate the starting diverse DCL as the system is still under thermodynamic exchange. Once the system is kinetically stable, the template may be removed to afford a library of candidates that may exhibit the desired/designed properties without themselves regenerating the DCL. Since the influence of templating on the product distribution of DCLs hinges on the molecular recognition between the template and library member(s), the conditions required to effect exchange must be compatible with the binding events within the system. Generally, this requirement precludes working at elevated temperatures and needs tolerance of a large number of functional groups.

The balance between kinetic lability and stability is delicate. Many reversible reactions have been explored as candidates for dynamic combinatorial chemistry including transimination, disulfide exchange, peptide formation and hydrolysis, and allyl ester exchange. Transimination of carbon–nitrogen double bonds in imines, oximes, and hydrazones, has received considerable interest in the field of DCC. Imine exchange is a well known reaction and indeed has been much used to form cyclic ligands for transition metals (see Section 3.1).^[166]

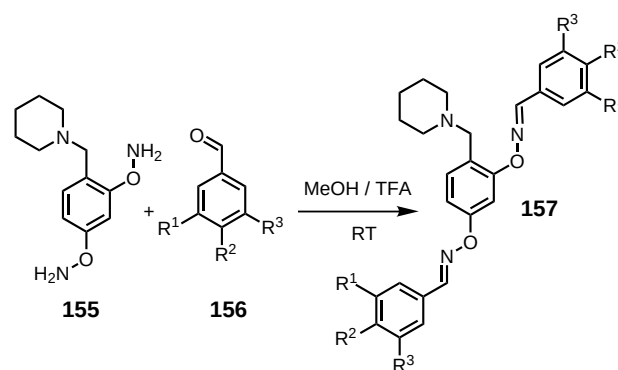
Imines were first explored in a dynamic combinatorial context in 1997 by Huc and Lehn,^[160] who described a virtual combinatorial library of imines whose composition is influenced by the presence of carbonic anhydrase (CA) as a “molecular trap”. A library of 12 imines and the 7 parent compounds was prepared in the presence of CA (Scheme 72),



Scheme 72. Formation of a DCL of imines from four amines and three aldehydes.

from which a casting process was observed. In the spirit of the “lock and key” principle, the concentration of the preferred target key **154** was amplified roughly twofold in the presence of CA, compared to the control experiment. In a second experiment, the library was prepared in the presence of CA and hexyl 4-sulfamoylbenzoate. The inhibitor reduced the influence of the enzyme on the DCL product distribution, which suggests that the binding site of CA is responsible for the ligand amplification observed. It should be noted, however, that the analysis has been performed on a “static” combinatorial library. Imines exchange freely at room temperature, often without the need for any catalysis, and so the DCL can be reinstated in the absence of CA. Thus, reduction of the imines using sodium cyanoborohydride was required before the analysis of the new library composition was performed.

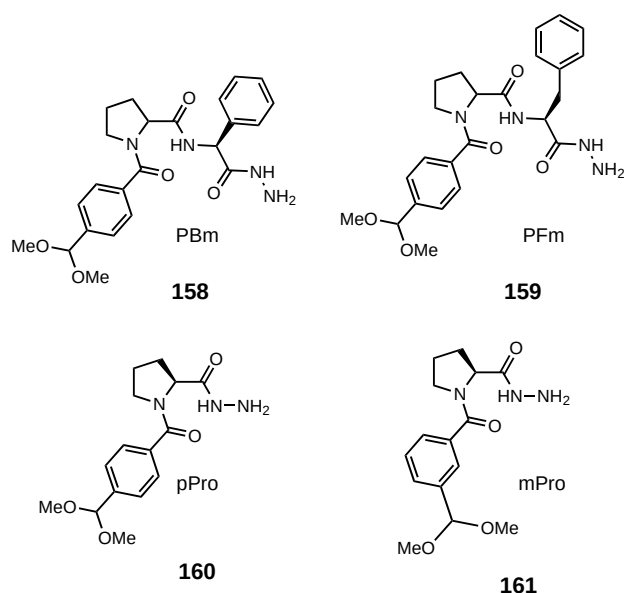
It is widely accepted^[167] that the carbon–nitrogen double bond of imines must be reduced to provide kinetically stable products. However, stabilized imines, in the form of oximes and hydrazones,^[168] have since attracted great interest for DCC as they can provide kinetically inert products without the need for subsequent reduction and the attendant change in geometry and electronics. Eliseev and co-workers^[169] have explored the use of *O*-aryl (**157**) and *O*-alkyl oximes to construct DCLs. The design is based on a common aromatic scaffold functionalized with two aminoxy groups (**155**), to which are condensed (Scheme 73) a pool of aromatic aldehydes (**156 A–K**). A full combinatorial library using all of the building blocks is not reported since mass similarities of the products do not allow unambiguous characterization of the library. Instead, analysis of sublibraries implies that all of the possible products are thermodynamically and kinetically accessible in the complete combinatorial pool. The authors have also reported an extensive kinetic study of oxime exchange and were able to conclude that exchange in water requires elevated temperatures (60 °C).^[170]



	R ¹	R ²	R ³		R ¹	R ²	R ³
A	H	H	H	G	H	OH	OH
B	H	H	OH	H	H	OH	OEt
C	H	OH	H	I	H	OMe	OH
D	H	OH	Me	J	H	NHAc	H
E	Me	OH	Me	K	H	OAc	H
F	OH	Me	OH				

Scheme 73. Formation of an oxime-based DCL.

The formation of diverse dynamic combinatorial libraries of pseudopeptide macrocycles using hydrazone exchange^[171] has proven to be remarkably successful. Hydrazone exchange proceeds under mildly acidic conditions at room temperature and is simply “switched off” by removal of the acid. Therefore, in comparison with imines and oximes, hydrazones offer the advantages of room-temperature exchange and kinetically stable products at high pH values. A series of amino acids, **158–161**, were adorned with a dimethoxyacetal-protected formyl group and a hydrazide functionality. Treatment of these building blocks with TFA catalyzes the deprotection of the aldehyde and subsequent hydrazone exchange. Treatment



of the monomers **158** and **159** (5 mM) individually with TFA affords wide distributions of cyclic species, which range from the cyclic monomer to at least the cyclic 13-mer, as detected by mass spectrometry. Although this diversity from one building block is impressive, the mixing of more than one building block results in an explosion of combinatorial diversity. A library containing more than 130 detectable cyclic species (up to cyclic undecamers) is formed from just two amino acid building blocks (Figure 19). Furthermore, the combinatorial diversity extends beyond the combinations identified by mass spectrometry.

By using this hydrazone chemistry, there is also scope for isomerism to be expressed at the configurational (*cis-trans*), conformational, and constitutional levels. For example, a pentamer (A_3B_2), formed from building blocks A and B, has two unique constitutional isomers *cyclo-AAABB* and *cyclo-ABABA*. Tandem mass spectrometry (MS-MS) has been used to demonstrate^[172] that sequence isomers are present in DCLs of hydrazone-based pseudopeptides. Reversibility has been demonstrated by the mixing of two individually preformed libraries of **158** and **159**. Although each library shows no presence of monomer or linear species on mixing, the hydrazones are able to exchange to generate a fully mixed DCL. If separate libraries of cyclic **158** and **159** are treated with triethylamine, the exchange is halted and mixing of the two solutions does not afford any mixed cyclic oligomers.

Hydrazone-based pseudopeptide DCLs have yielded some of the most striking examples of templating in DCC. The monomer **161** forms a range of kinetic intermediates from cyclic dimer to cyclic 15-mer when cyclized under conditions of mild catalysis. Subsequently, they undergo thermodynamic proof-reading to afford predominantly the cyclic dimer (>90%). More significantly, the introduction of *N*-methylammonium salts to this DCL results in a change in the product distribution to afford a single conformer of cyclic trimer **162** as the major species (Scheme 74).^[173]

A shift towards 90% cyclic trimer has been observed when the neurotransmitter acetylcholine (**163**) is used as the

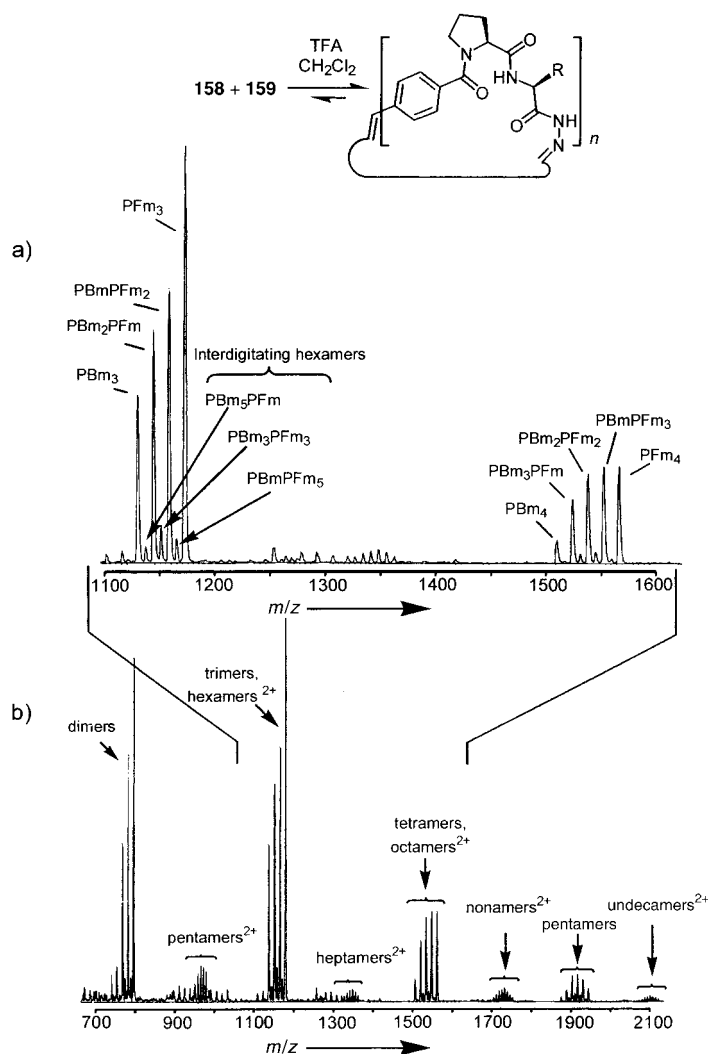
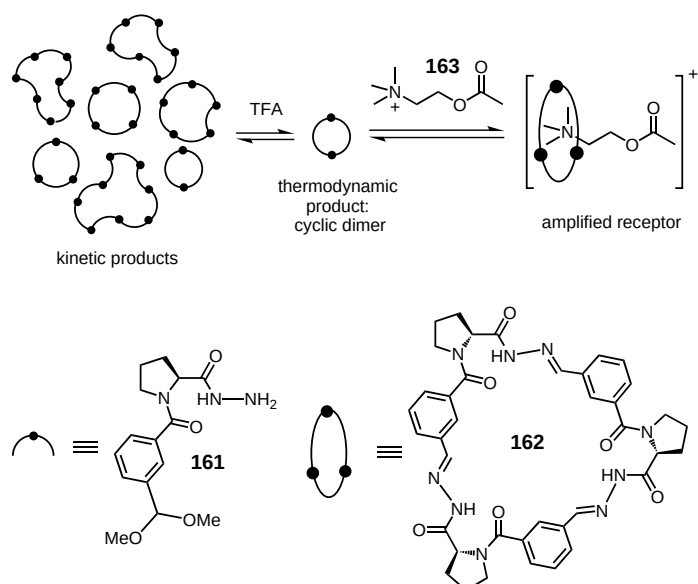


Figure 19. a) An expanded region of the mass spectrum recorded for a mixed cyclization of **156** and **157**; b) the complete mass spectrum recorded from m/z 700–2100.

template. Binding between the template and cyclic trimer has been confirmed by NMR spectroscopy and mass spectrometry (Figure 20). The DCL adjusts to amplify 50-fold a receptor that is initially present as only a minor species in the combinatorial library when acetylcholine is used. It is to be expected that extending the diversity to feature more building blocks will lead to the identification of better receptors for acetylcholine, and indeed for other biologically important molecules.

Experiments carried out by Furlan et al.^[174] using the **160** library demonstrated the ability of [18]crown-6 to influence the product distribution. [18]Crown-6 forms a complex with the protonated hydrazide terminus of linear intermediates of the hydrazone macrocycle **164** exchange and results in the amplification of the **165**·[18]crown-6 adduct (Scheme 75). A species that, in the first instance, is present at such low concentrations as to be undetectable by HPLC and mass spectrometry becomes a major component of the DCL (67%) after addition of the crown ether. The original product distribution may be reinstated by the introduction of potassium ions (as KBr) which bind competitively to the [18]crown-6.



Scheme 74. A schematic representation of the cyclization of **161** and subsequent proof-reading and templating of the DCL. Proof-reading affords the thermodynamically favored cyclic dimer as the major product, while the introduction of **163** templates the formation of a receptor for itself, namely, the cyclic trimer.

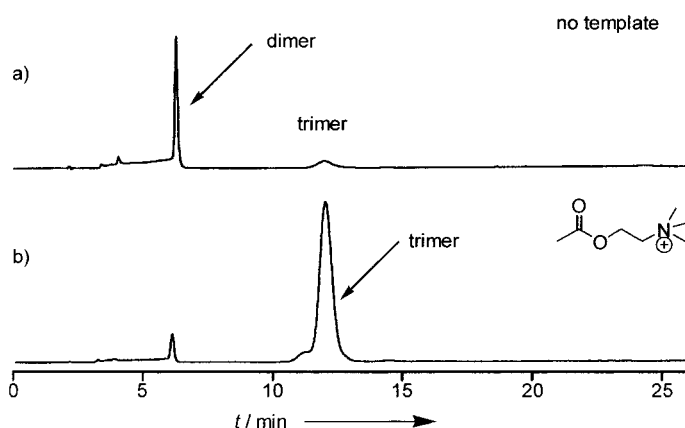
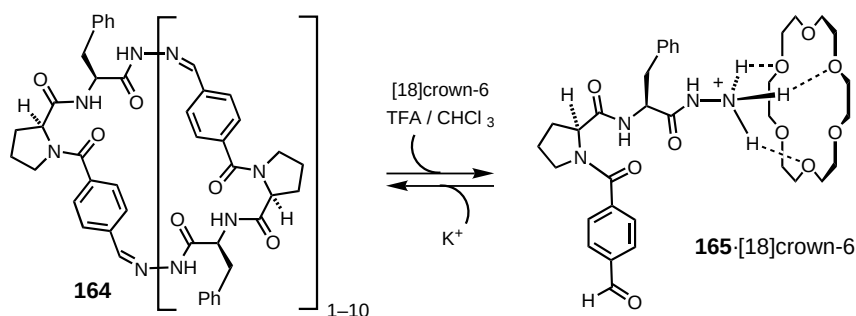


Figure 20. a) HPLC trace for **161** cyclized in the absence of template for 2 days. b) Cyclization of **161** in the presence of 2 equivalents of acetylcholine **161** under the same conditions.



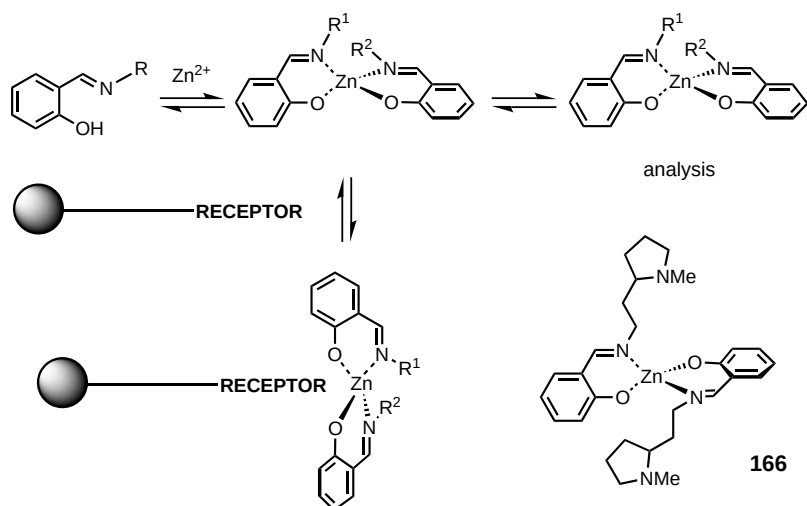
Scheme 75. Molecular amplification of the linear monomer (formed from **164**) by introduction of [18]crown-6 to form **165**·[18]crown-6. The original product distribution may be re-established by the introduction of potassium ions.

Furthermore, addition of Li^+ ions to dynamic libraries of macrocycles of **164** has allowed a one-pot synthesis and isolation on a preparative scale of a new receptor for Li^+ ions.^[175] The receptor **164** ($n = 3$), which is equivalent in size to a cyclic nonapeptide, is rather flexible, and it changes its conformation on binding, so it would have been particularly difficult to create by design. This study illustrates the potential of the dynamic combinatorial approach for the discovery of new, unpredictable receptors.

Hydrazone exchange is clearly emerging as an ideal vehicle for dynamic combinatorial chemistry. The exchange is rapid and proceeds at room temperature in the presence of a catalytic amount of TFA.^[176] Ultimately, combinatorial diversity and templating are easily achieved from simple building blocks with hydrazone-based systems. The synthesis of building blocks functionalized for hydrazone-based DCL formation is straightforward and widely applicable. Indeed, hydrazone DCL chemistry has been explored with cholic acid-scaffolds with some considerable success.^[177]

The relative degree of amplification in the dynamic library will depend on the difference in binding affinity of the library components to the template. A recent theoretical analysis by Moore and Zimmerman^[178] of the effect that a subset of ligands with different binding constants has on the sequence of a dynamic copolymer did confirm that the equilibrium could be shifted. However, the amplification in such a system would be limited to about two orders of magnitude on account of competitive binding from the larger number of weaker binders. While this may be enough for initial identification of the ideal binder, synthesis of this desired compound may have to be achieved by more conventional means. This result suggests that careful planning of the library may be necessary with components that contain high functional diversity and distinctly different projected affinity to the substrate. Another approach may be to use some sort of kinetic-based amplification procedure to shift the equilibrium.^[80]

The challenge is to identify molecules with more wide ranging molecular function and greater interest, perhaps from more diverse combinatorial libraries. One approach is to use solid-phase supported templates or reagents to select lead compounds from diverse DCLs. For example, resin-immobilized, double-stranded DNA has been successfully used to identify high affinity ligands for homopolymeric double-stranded DNA.^[179] An equilibrating mixture of 36 bis(salicylaldiminato)–zinc complexes formed by condensation of an aldehyde and amine was incubated with a cellulose resin bearing oligo(dT·dA) double-stranded DNA (Scheme 76). Elution gave a mixture of products that differed in distribution from the control library. A decrease in concentration of a given member would imply that the library member is still bound to the resin. Indeed, complex **166** was identified in this experiment as a strong binding ligand for DNA as a result of solution-based binding studies of the successful candidate and the unsuccessful compounds.



Scheme 76. The generation of an equilibrium mixture of bis(salicylaldiminato)zinc complexes. The broad spectrum of substituents R is the origin of combinatorial diversity.

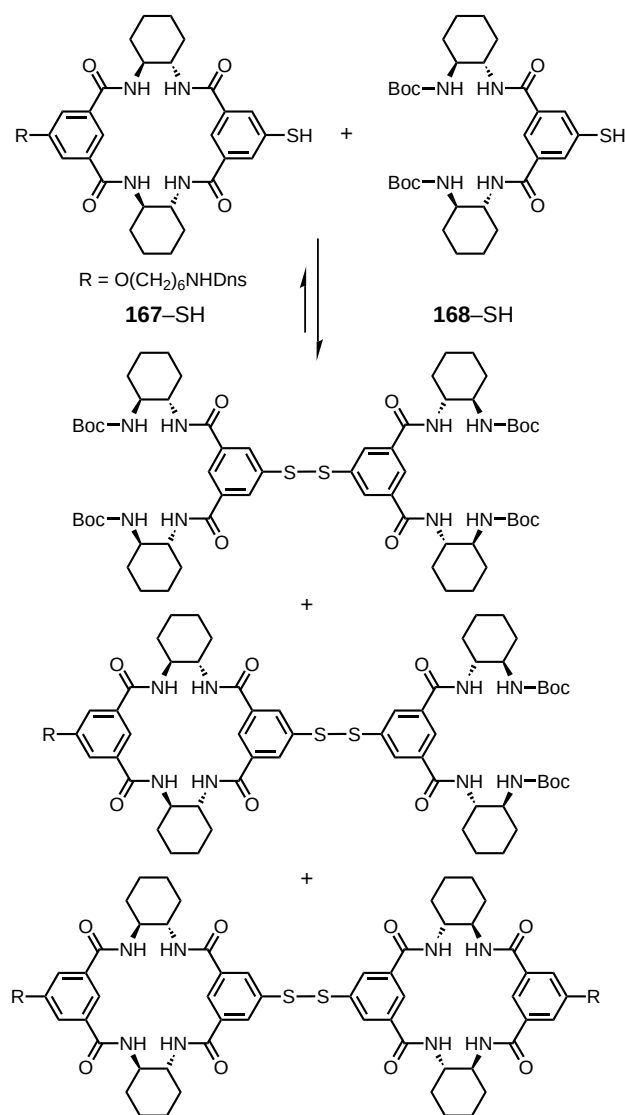
Disulfide exchange^[180] is also a promising candidate for dynamic combinatorial chemistry. Although, disulfides undergo rapid exchange at moderate to high pH (≥ 7), the bond is kinetically stable at low pH (< 5), thus providing stable disulfide products. The reaction was first explored explicitly in a dynamic combinatorial capacity by Hioki and Still^[181] who developed a strategy for selecting and amplifying a receptor for the tripeptide (D)Pro(L)Val(D)Val. These authors drew on previous work, in which molecules containing linked oligomers of isophthalic acids and *trans*-1,2-diamines were identified as highly sequence-selective receptors for peptides,^[182] to develop an analogous DCL strategy. Two thiol derivatives were synthesized that are based on receptor cores of cyclic oligomers of isophthalic acids and *trans*-1,2-diamines, namely **167** and **168** (Scheme 77).

From these two thiols were formed the mixed disulfide **167-SS-168**, for which no binding to the polymer-bead-supported tripeptide (D)Pro(L)Val(D)Val-PS was observed. When **167-SS-168** was equilibrated in the presence of **168-SH**/Et₃N, the homodisulfide products were formed and the equilibrium constant for the exchange reaction was 1.8. In the presence of (D)Pro(L)Val(D)Val-PS, the equilibrium was shifted in favor of the peptide-binding **167-SS-167** receptor ($K = 32$ versus 1.8 for the template-free reaction). Importantly, the fact that the peptide sequence template was supported on a polymer resin allowed purification of the peptide receptor. Washing of the substrate-carrying beads with CHCl₃ eluted all of the unbound material and then finally a wash with DMF extracted the peptide-binding receptor in 97.5% purity.

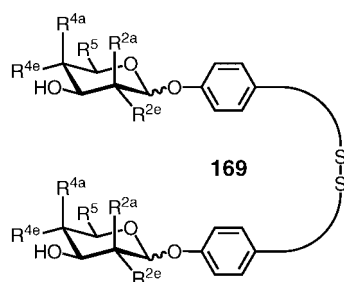
Disulfide exchange may also be performed in water, thus providing access to many biomimetic systems. Very recently, Ramström and Lehn^[183] have used disulfide exchange to develop a system closely related to the casting performed using carbonic anhydrase on an imine-based DCL. In this example, lectin concanavalin A (ConA) was used to amplify a carbohydrate guest from a pool of disulfide-linked sugar residues **169** (Scheme 78). ConA appended to sepharose beads was introduced to a library of 21 components formed from the exchange of six disulfide-linked carbohydrate

dimers. Comparison of HPLC analysis of the solution of unbound species and a solution of hosts eluted from the beads showed considerable amplification of the mannose–mannose dimer and also a change in concentration of all the possible mono-mannose-containing dimers. This protocol showed that the D-mannose homodimer was the entity most efficiently bound to the lectin.

The establishment of greater diversity using disulfides is the subject of work reported by Otto et al.^[184] who used a collection of dithiol building blocks **170–173** to generate (Scheme 79) DCLs of macrocyclic disulfides. FT-ion-cyclotron resonance (ICR)/electrospray ionization (ESI) MS analysis identified over 100 macrocycles of unique mass/charge ratios. In some cases, they are separated by only 0.17 amu. In addition to illustrating the



Scheme 77. Two thiols **167-SH** and **168-SH** and their subsequent DCL formation. From this DCL is identified a receptor for tripeptide D-Pro-L-Val-D-Val.



Compound	α/β	R ^{2a}	R ^{2e}	R ^{4a}	R ^{4e}	R ⁵
Man/Man	α	OH	H	H	OH	CH ₂ OH
GalC ₂ /GalC ₂	β	H	OH	OH	H	CH ₂ OH
GalC ₃ /GalC ₃	β	H	OH	OH	H	CH ₂ OH
Glc/Glc	β	H	OH	H	OH	CH ₂ OH
Ara/Ara	β	H	OH	OH	H	H
Xyl/Xyl	β	H	OH	H	OH	H

Scheme 78. Structures for some disulfide-linked sugar dimers **169** formed in the disulfide library by Lehn and Ramström,^[183] used for identification of new ligands for lectin ConA. Man = D-mannose, GalC₂ = D-galactose-(CH₂)₂, GalC₃ = D-galactose-(CH₂)₃, Ara = L-arabinose, Xyl = D-xylose.

hydrolysis of peptide bonds) is used to generate a DCL of short peptide sequences, thus adding amide exchange to the repertoire of reactions available to the dynamic combinatorial chemist. Incubation of Tyr-Gly-Gly and Phe-Leu with thermolysin generated a mixture of 15 peptides. The same experiment carried out in the presence of a monoclonal antibody able to recognize Tyr-Gly-Gly-Phe-Leu (YGGFL) was expected to show an increase in the concentration of YGGFL. However, the amount of YGGFL formed in the reaction saturated the antibody because the low concentration of antibody used. Therefore, although ligand amplification could not be proven directly, the mixture did inhibit modestly the binding of radiolabeled β -endorphin to the antibody, thus indicating that the antibody behaves as a molecular sink for YGGFL.

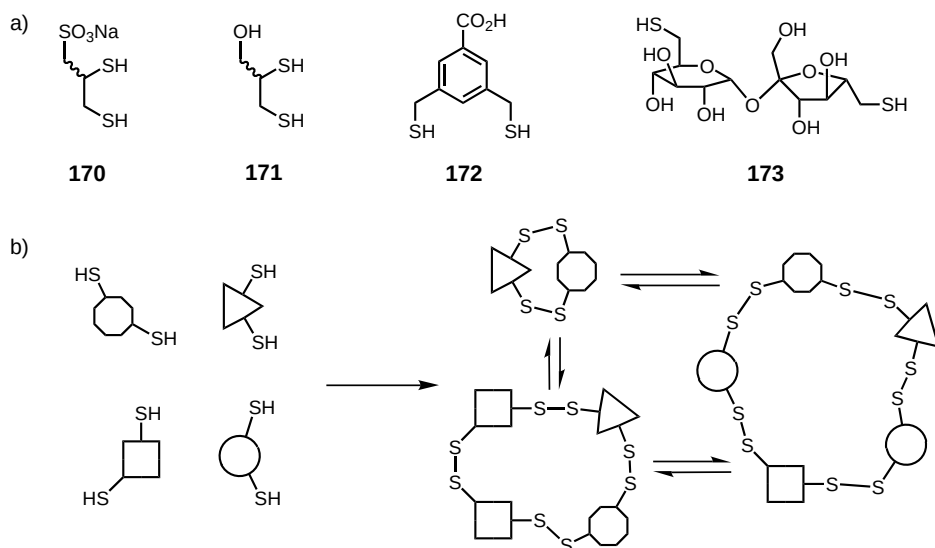
In a similar experiment, incubation of fibrinogen with a mixture of trypsin hydrolysates of the bovine serum albumin thermolysin and a tripeptide Gly-Pro-Arg revealed two tetrapeptides, Gly-Pro-Arg-Leu and Gly-Pro-Arg-Phe, that bound weakly to fibrinogen. Conceptually, this approach offers a powerful method for generating new peptides with important biological properties. At present, however, the ability to establish effective reversible peptide bond formation puts a severe constraint on such strategies.

Recently, Basso et al.^[186] reported the thermodynamically controlled synthesis of dipeptides using thermolysin absorbed onto celite. This approach allows peptide formation to occur in organic solvents, such as toluene, while maintaining water for enzymatic activity within the celite matrix. The conditions and yields of this reaction offer much promise for the generation of DCLs of peptides and their subsequent templated synthesis. It is possible that other enzymatic reactions, such as ester exchange using lipases, will find application in DCC, provided that the problem of substrate specificity is not too difficult to overcome.

A reaction that may receive interest in the future for DCC is alkene metathesis. Ring-closing metathesis

for the synthesis of macrocyclic alkenes from acyclic diene precursors has emerged^[187] as a powerful technique, which has been made possible by the discovery of metal-carbene catalysts which can tolerate a wide range of functional groups (Section 2.1). Examples of the application of alkene metathesis to dynamic combinatorial synthesis are few and far between. Recently, Nicolaou et al.^[188] have used olefin chemistry to ligate vancomycin derivatives and establish a combinatorial library of vancomycin dimers. Combinatorial diversity is achieved by varying the chain lengths of the linkers and changing the functional groups of the vancomycin derivatives.

Vancomycin dimers are biologically important, with back-to-back dimerization of vancomycin strengthening the hydro-



Scheme 79. a) Dithiols **170–173** used by Otto et al.^[184] to form a DCL of disulfide macrocycles. b) Schematic representation of DCL formation and exchange.

applications of FT-ICR/ESI-MS to DCC, this report illustrates exchange, as well as an ability to switch-off exchange, of disulfides. The system is yet to be used to identify novel receptors in selection and amplification experiments.

Oligomeric disulfides offer an additional dimension of diversity since they are omnidirectional in contrast with carbon–nitrogen double bond systems, that is, an asymmetrical dithiol may be connected in both an **AB** and a **BA** fashion, which gives rise to directional constitutional isomers.

Amide bonds, although typically robust chemical functionalities that are resilient to a wide range of chemical conditions, have potential in DCC. Swann et al.^[185] have reported a system in which thermolysin (a nonspecific protease that, under appropriate conditions, catalyzes both the synthesis and

gen-bonding interaction between the vancomycin framework and the D-Ala-D-Ala moiety. Ligation of eight vancomycin derivatives affords 36 components of the library. When the ligation is performed in the presence of Ac₂-L-Lys-D-Ala-D-Ala, the dimers that bind well to the substrate are amplified in the combinatorial library, and are thus favored. General trends were identified for the strong binding of the substrate, for example, short tethers and LeuNMe as the first amino acid residue of vancomycin. Gratifyingly, three dimers were amplified in the combinatorial library and determined to be highly potent antibacterial agents. In the same report, a model library based on disulfide ligation was also mentioned. However, there is no direct evidence that the products from these vancomycin combinatorial libraries are under thermodynamic exchange and the result reported in the literature may well be the result of kinetic acceleration. Despite these doubts, the potential of such systems is considerable.

The application of alkene metathesis to DCC will be highly dependent on the catalysts available. Currently, the rates of metathesis and lifetimes of the catalysts available are not conducive to template-directed screening in DCLs. However, the situation is already changing as more efficient catalysts for olefin metathesis (such as **11**) emerge on the scene.

The examples reviewed so far highlight the successes of dynamic combinatorial chemistry using reversible covalent bonds. They illustrate some of the key concepts, such as exchange, combinatorial diversity, thermodynamic proof-reading, and templating. Hydrazone and disulfide exchange are, to date, the most successful exchange reactions with conditions of exchange that are amenable to DCC. Both afford highly diverse DCLs and express kinetic lability combined with an ability to “switch-off” exchange. So far, hydrazone chemistry has provided some of the most dramatic examples of template control over DCL product distributions. We have met the key requirements of a reversible covalent reaction for DCC. They include kinetic lability—under conditions compatible with molecular recognition events and a wide range of chemical functionalities—and kinetic stability to provide isolable products and widely applicable chemistry for the synthesis of building blocks.

DCC is in its infancy: many future investigations are to be expected, while new reactions for the generation of DCLs are now emerging. These reactions include palladium-catalyzed allyl ester exchange,^[189] dioxadiazadecalin/salen tautomeric macrocycles,^[190] boronate ester formation,^[191] and boraza-aromatic macrocycles.^[192] The cyclodepolymerization of linear esters has also been reported.^[61] All these reactions and examples have their own advantages, disadvantages, and potential applications. Here, the key concepts of DCL generation, diversity, and templating have all been addressed in the systems presented.

5. Reflections and Perspectives

Dynamic covalent chemistry is nothing new. It has been around for a century or more and has been part and parcel of the reactivities of carbohydrates and polymers from the times

chemists started to investigate them seriously. It is the emergence, in more recent times, of some new lines in chemistry, such as those carrying the combinatorial and supramolecular labels, that has sparked off a revival in dynamic covalent chemistry. The sharp rise in our appreciation of the importance of self-assembly processes (both in their own right and together with those that are followed by some further consolidation of the resulting order) which has accompanied our increased knowledge of and reliance on coordinative and noncovalent bonds for the construction of highly ordered aggregates and arrays with precise architectures, has rekindled our interest in chemical systems that form spontaneously and take shape, often gradually under equilibrium control.

It is hardly surprising that we seek to do chemistry involving the making and breaking of covalent bonds under thermodynamic control. Covalent bonds suggest a bonding situation in molecular substances that is potentially more robust than we would normally anticipate following the formation of supramolecular species using noncovalent bonds, unless they become extremely numerous and highly cooperative. There is also the attractive prospect of “fixing” dynamic covalent bonds when the time is ripe, which gives us the best of both worlds in terms of efficient thermodynamic control and the security that comes with kinetic control.

Dynamic covalent chemistry comes into its own when it is carried out in the presence of templates, whether they are recycled or captured (and hence consumed) in the process. The covalent synthesis of macrocycles and capsules is often achieved in the presence of a temporary template, whereas catenanes and rotaxanes can be the outcome of templation which is temporarily (magic rings and rods!) under a thermodynamic regime and only become permanent under a kinetic one.

The potential to build highly complex, covalently bonded architectures (for example, those based on the Platonic polyhedra) could become routine, given access to the “correct” building blocks. It should be noted, however, that the efficiencies of such thermodynamically controlled processes are limited only by the free energy advantage the desired product enjoys with respect to all its different possible contenders. In other words, to make the most of a dynamic approach to synthesizing molecules, it is necessary to establish significant thermodynamic gradients in favor of the desired product to ensure its efficient production. The judicious choice of building blocks and/or the use of templates may be employed to achieve this end. Additionally, it must always be remembered that it is also possible to achieve extremely high yields in the synthesis by simply employing a final kinetically controlled process, for example, a crystallization or a reaction, to milk the thermodynamically controlled process for all its worth.

Simple and elegant as they can be in practice, the development of dynamic combinatorial libraries is another one of the more appealing aspects of dynamic covalent chemistry performed in a contemporary setting. The chance to allow building blocks at equilibrium to pick and choose the best template is an extremely attractive game to play. It allows a better fundamental understanding to emerge of how and why

molecules come together and recognize each other. The potential for such a system to adjust its product distribution in response to changes in its immediate environment opens up the possibility of producing adaptable ("smart") materials which can alter their molecular structures and hence mechanical and functional properties in response to a particular stimulus (for example, temperature, light, or, indeed the presence of another (hazardous) chemical compound).

These two characteristics constitute the different sides of the coin in dynamic covalent chemistry: one requires rigid pre-organized and pre-disposed building blocks to effect the efficient synthesis of a molecular structure, while the other requires the flexibility within and between the building blocks to allow access to a variety (library) of molecules. Careful planning has to go into the design of these flexible building blocks prior to doing any dynamic covalent chemistry with them; for example, a completely rigid building block is only useful in the construction of a molecular structure if the reactive functional groups adopt the appropriate relative orientations with respect to each other. A small amount of flexibility is desirable in the building blocks to give the molecules a chance to sample slightly different conformations in the search for thermodynamic wells.

At least two lines of current chemical research are crucial for the furtherance of dynamic covalent chemistry: 1) the identification of "new" dynamic covalent bonds and 2) the development of catalysts which promote the fast exchange of covalent bonds, yet display high functional group tolerance.

Put rather simply, dynamic covalent chemistry offers the possibility of "doing supramolecular chemistry" at the level of covalent bonds. It is complementary to the wide range of elegant, kinetically controlled, covalent chemistry that has evolved over the years. With only a few exceptions, it has lagged behind because it is not suited to the synthesis of small molecular weight compounds. As the attention of synthetic chemists turns more and more to larger molecular weight compounds, however, dynamic covalent chemistry will come more and more into the limelight.^[193]

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Palladium-Catalyzed α -Arylation of Esters: Ideal New Methodology for Discovery Chemistry**

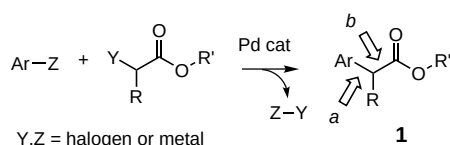
Guy C. Lloyd-Jones*

" α -Aryl carboxylic acids and α -aryl amino acids are amongst the most important carbonyl compounds."^[1]

"The synthesis of α -aryl esters and their derivatives is of interest in organic chemistry."^[2]

"Methylenecarboxy groups are key functionalities in many biologically active compounds."^[3]

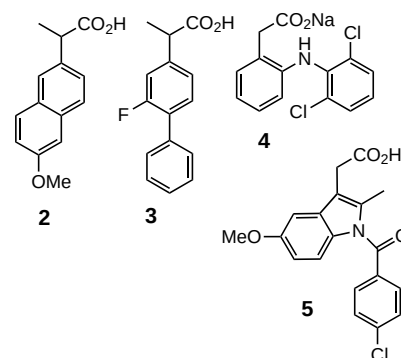
These are the opening statements from Hartwig et al.,^[1] Buchwald et al.,^[2] and Gooßen^[3] in their recent disclosures of new methods for generating Ar-C(R)H-CO₂R' units **1** by palladium-catalyzed formation of the Ar-C _{α} bond (bond 'a', Scheme 1).



Scheme 1. A useful route to α -arylated esters and amino acids (R = NH₂), by formation of bond *a*. Most current synthetic methods involve formation of bond *b*.

These overtures are justified: a wide range of substituted arylacetic acids are of significant commercial importance as 'NSAIDs'.^[4] Examples include naproxen (**2**), flurbiprofen (**3**), dichlofenac (**4**), and indomethacin (**5**).

The majority of synthetic routes to α -aryl acetic acids **1**^[5] and α -aryl α -amino acids^[6] involve construction of the 'b' bond (Scheme 1). Consequently, arylation-type routes (constructing bond *a*, Scheme 1) should be valuable weapons in the synthetic chemists' armory. However, the few examples



that are known^[7] have not been widely adopted; this may be for a variety of reasons including expense, lack of generality, or operational complexity.

Palladium-Catalyzed α -Arylation Reactions

In contrast to other α -arylation routes, the novel methodologies recently reported by the Hartwig, Buchwald, and Gooßen groups are likely to become popular: they proceed in high yield, under simple conditions, and employ readily available substrates and reagents (Scheme 1; Z = BR₂ or halide, Y = Br or H); this Highlight focuses on these important developments.

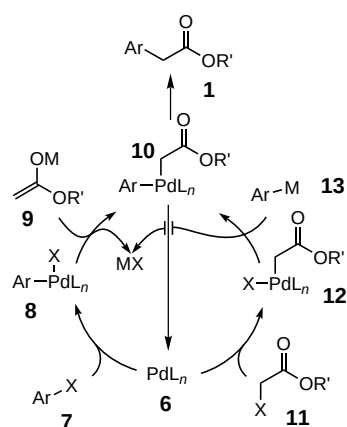
The approach of Hartwig et al., and Buchwald et al. for the generation of **1** is essentially identical and involves the Pd-catalyzed reaction of an aryl halide (**7**) with an ester enolate (**9**; Scheme 2, left-hand half of the catalytic cycle). Common ground with the Gooßen approach (right-hand half) is found in the Pd⁰ complex **6** and the proposed palladium-enolate^[8] intermediate **10**, generated in an alternative fashion from a bromoacetate (**11**) and an aryl boronate (**13**). In either procedure, reductive elimination in **10** forms the *a* bond of **1** and regenerates the Pd⁰ species **6** to facilitate further turnover of the catalytic cycle.

On first inspection, both routes appear simple and promising. However, as is often the case in the rather subtle science of catalysis, both systems presented a number of obstacles that needed to be overcome.

In the Hartwig-Buchwald system, the requisite enolate **9** is generated by deprotonation of the corresponding ester. This

[*] Dr. G. C. Lloyd-Jones
School of Chemistry
University of Bristol
Cantock's Close, Bristol BS8 1TS (UK)
Fax: (+44) 117-929-8611
E-mail: Guy.Lloyd-Jones@bris.ac.uk

[**] Dr. Lukas J. Gooßen (MPI, Mülheim) kindly provided details of attempted α -bromo propionate arylation. I thank the RSC (Hickinbottom Fellowship), Pfizer Ltd, and AstraZeneca for generous and unrestricted research support.

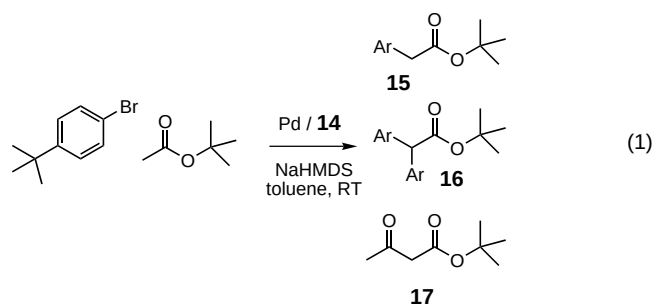


Scheme 2. Potential Pd-catalyzed routes to α -arylated esters **1**. Left-hand of cycle: Hartwig and Buchwald's arylation via enolate ($M = \text{Na}, \text{Li}$) trapping of Ar-Pd intermediate (**8**, $X = \text{Br}, \text{Cl}$); right-hand of cycle: Gooßen's route involving arylative transmetalation (with **13**, $M = \text{B}(\text{OR})_2$) of a Pd -enolate (**12**, $X = \text{Br}$).

method opens the door to an undesired reaction between enolate and ester resulting in Claisen products (acetoacetates). Accordingly, hindered *tert*-butyl esters were employed to suppress nucleophilic attack at the carbonyl carbon atom. As with aryl amination, the choice of ligand and base^[9] is crucial and since Na-derived bases had earlier proved superior in amination reactions, NaHMDS (HMDS = 1,1,1,3,3,3-hexamethyldisilazane) was the first choice.

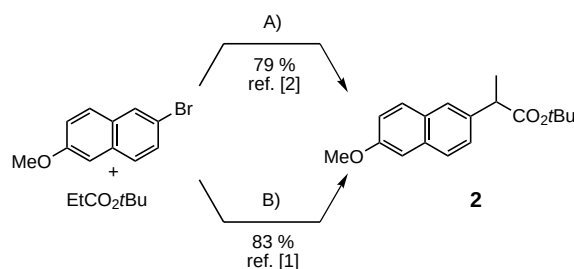
The Buchwald Approach

The Buchwald group employed their biaryl ligand **14** and obtained a 46% yield of mono- and diarylated acetates (**15** and **16**) together with competing Claisen product **17**, on reaction of *tert*-butyl acetate with *p*-*tert*-butyl bromobenzene [Eq. (1)].



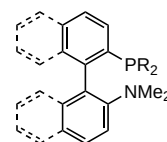
The mixture of mono- and diarylation represents the second problem: the primary product (here, **15**) is more acidic than the *tert*-butyl acetate and thus the acid–base equilibrium will facilitate a second arylation leading to **16**. This problem was controlled by switching from an Na to an Li counterion (LiHMDS),^[10] by using this method a wide range of aryl bromides underwent coupling with *tert*-butyl acetate in toluene at ambient temperature, in yields that ranged from 71–90%. Importantly, the extensively competing Claisen reaction required the use of a large excess of enolate (2.3 equivalents of *tert*-butyl acetate and 2.5 equiv-

alents of LiHMDS) and thus yields based on ester are significantly lower. Propionates and higher homologues also reacted smoothly, although, again a large enolate excess is required. The procedure is very versatile, for example, the *tert*-butyl ester of racemic naproxen (**2**) is obtained in 79% yield after 15 h at ambient temperature (Scheme 3A).

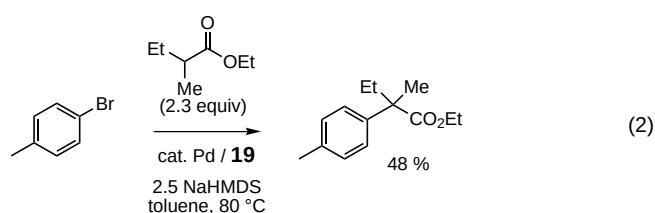


Scheme 3. Buchwald (A) and Hartwig (B) routes to the *tert*-butyl ester of naproxen (**2**). Conditions A) 2.3 equivalents EtCO_2tBu ; 2.5 equivalents NaHMDS; 3 mol % $\text{Pd}(\text{OAc})_2$; 6 mol % **19**; toluene, RT, 15 h. B) 1.1 equivalents EtCO_2tBu ; 2.3 equivalents NaHMDS; 1 mol % $\text{Pd}(\text{dba})_2$; 1 mol % **20**; toluene, RT, 12 h; dba = *trans,trans*-dibenzylideneacetone.

Often unpredictably, the choice of ligand in Pd-catalyzed reactions can make surprisingly little difference or can open up new avenues. In the current case, the latter situation prevails. There has recently been much attention given to finding methods for the use of cheaper aryl chlorides in place of bromides or iodides in Pd-catalyzed couplings. Using the ligand **14**, poor results were obtained with 4-chloro-aromatics in the ester arylation reaction, but on switching to the *t*Bu₂PAr analogue (**18**) the reaction proved feasible. Furthermore, with the binaphthyl-based ligand **19**, even α -dialkylated acetates could be arylated (albeit only using aryl bromides) so as to generate quaternary carbon centers [Eq. (2)].

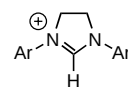


14 benzo, $R = \text{Cy}$
18 benzo, $R = t\text{Bu}$
19 naphtho, $R = t\text{Bu}$



The Hartwig Approach

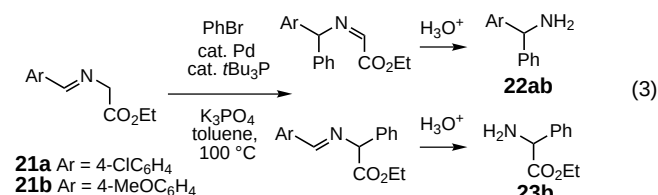
In contrast to the P,C-based ligands (**14**, **18**, and **19**) employed by the Buchwald group, Hartwig et al., chose to use a carbene ligand^[11] generated in situ from hindered dihydro imidazolium **20**. Furthermore, they employed an excess of base. In fact a whole extra equivalent of base (Li- or NaHMDS) was added to only 1.1 equivalents of ester so as to deprotonate the product as it is generated. This cunningly solves three problems: first, the Claisen reaction is sup-



20 Ar = 2,6-*i*Pr₂C₆H₃

pressed since this requires non-enolized ester coreactant; second, the more reactive (but less acidic) ester reagent can now compete effectively with the product for arylating agent and thus double arylation is suppressed; third, the reaction no longer requires an excess of ester reagent and thus the yields are good based upon both components. The choice of base again proved important: LiHMDS functioned well with acetates whilst NaHMDS worked well with propionates.^[12] In both cases, excellent yields (75–98%) were obtained with a range of aryl bromides (Scheme 3B).

By slightly modifying the conditions (employing *t*Bu₃P as ligand and K₃PO₄^[13] as base) *N*-protected glycines undergo analogous arylation. Benzophenone imine proved a suitable protecting group and allowed a large range of glycines to be arylated. The products are readily hydrolyzed on work-up and thereby facilitate direct access to C-protected α -aryl amino acids. However, the expensive nature of benzophenone imine led Hartwig et al. to explore the use of arylaldehydes (**21**). *N*-(4-chlorobenzylidene) glycinate (**21a**) is 'conveniently crystalline', however, reaction with bromobenzene gave two arylated products. The α -aryl-benzylamine (**22a**) was reasoned to arise from arylation of the "wrong" tautomeric enolate, [Eq. (3)]. Electronic tuning of the protecting group (using 4-methoxybenzylidene, see **21b**) shut down this pathway and thus provides, via **23b**, a general route to C-protected α -aryl glycines.^[14]

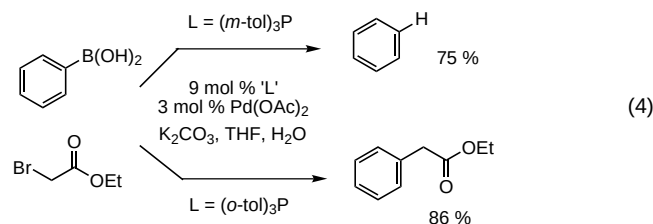


The Gooßen Approach

The switching of electrophile with nucleophile and vice versa, defines the Gooßen approach. Oxidative addition of a α -halo ester to a Pd⁰ species (see **6** in Scheme 1) should generate a neutral Pd^{II}-enolate species **12** bearing a coordinated halide counterion. Transmetalation with aryl–metal compound **13** then generates the requisite aryl–Pd enolate **10** primed for reductive elimination to yield the desired α -aryl ester **1**.

No complications because of acid–base equilibria are expected, a range of aryl boronic acids and α -halo esters are available and thus, in principle, this method appears advantageous. However, there are two problems that are apparent on further consideration. First, competing Pd⁰–Pd^{II}–Pd^{IV} cycles are known to facilitate reduction and reductive coupling of aryl boronic acids under analogous conditions^[15] and thus Ar–H and Ar–Ar are likely by-products. Second, palladium enolates of esters in which there is a β -hydrogen atom (i.e. propionates) are likely to undergo β -H elimination faster than they transmetalate and thus generate acrylates. The former, but not the latter, turned out to be readily solved by ligand tuning. Relatively bulky triaryl phosphanes facilitate the desired reaction and inhibit biaryl formation. Comparison of

the results obtained employing isomeric *meta*- and *ortho*-tritolylphosphane ligands illustrates the case rather well [Eq. (4)].



Ultimately, the best conditions were found to involve tri- α -naphthylphosphane as the ligand, with THF as solvent, K₃PO₄ as base, and water (2 equiv.) as coadditive (to facilitate boronate formation). Using these conditions, a wide range of aryl boronic acids were coupled in high yield with ethyl bromoacetate. Pd-catalyzed Suzuki–Miyaura type reactions of aryl halides with diboronates (R₂B–BR₂) or boranes (R₂B–H) have recently emerged as useful routes to aryl boronic acid derivatives.^[16] By connecting the two reactions, Gooßen went on to develop a very effective strategy for the formal hetero-coupling of aryl halides (or pseudohalides) with bromoacetates. The only current limitation with the Gooßen system is the restriction to bromoacetate. As expected, propionates divert by β -H elimination to yield acrylate esters.^[17] However, recent results from Fu et al.,^[18] suggest that these problems may not be insurmountable.

Summary and Outlook

Two new methods have been recently disclosed for α -arylation of esters. One route also provides ready access to α -arylated amino acids. Both methods are based on Pd catalysis and the choice of ligand is crucial. The two approaches are complimentary with regard to electrophile and nucleophile pairings.

Unless the catalyst efficiencies are increased phenomenally, the current price of Pd will preclude these methods from commercial production processes. Nonetheless, their generality and operational simplicity makes them ideal for discovery chemistry or lead development in the pharmaceutical or agrochemical industries. Since the requisite substrates (acetates and homologues, iminoacetates, aryl halides, and aryl boronates) are often items of commerce or very readily prepared, it should be anticipated that these new synthetic methods will find extensive application in combinatorial-type screening processes.

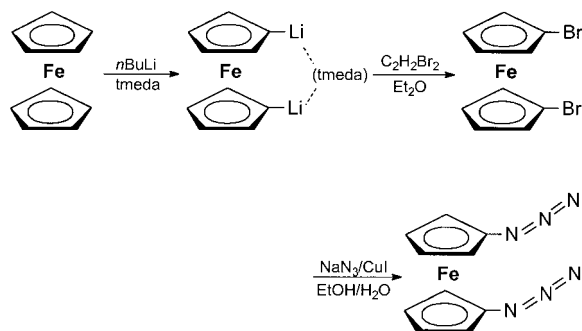
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- [5] For example by the Willgerodt reaction on the corresponding acetophenone.
- [6] For example by Strecker synthesis from the corresponding benzaldehyde.

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- [9] Note that the base employed must not bear a β -hydrogen (because of the potential for undesired Pd^{II} reduction by β -H transfer). *tert*-Butoxide bases proved sluggish whereas hexamethyldisilazide compounds proved useful.
- [10] It is not evident why this works, although there is some discussion of M–O (M = Na, Li) covalency. Perhaps surprisingly, given the reduction of diarylation on switching from NaHMDS to LiHMDS, ethyl phenylacetate can be α -arylated in good yield (based on arylating agent) at 80 °C under essentially the same conditions.
- [11] With very hindered aryl substrates, Hartwig et al., found that *t*Bu₃P proved to be better than the carbene ligand.
- [12] With hindered propionates (those with branching at the α - or β -positions) or glycinate, the ethyl, or methyl ester was preferred over the *tert*-butyl ester.
- [13] The higher C–H acidity of ketimine and aldimine derivatives of glycinate allows the weaker base K₃PO₄ to be employed.
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1,1'-Ferrocenedi(amido) Chelate Ligands in Titanium and Zirconium Complexes

Max Herberhold*

Although known for more than four decades,^[1, 2] the sandwich compound [Fe(C₅H₄-NH₂)₂] (**1**) ([fc(NH₂)₂]; fc = ferrocene-1,1'-diyl),^[2, 3] has not really been used either as a building block in polymers or as a chelate ligand in transition metal complexes. Recently, however, an improved synthesis—via 1,1'-di(azido)ferrocene ([fc(N₃)₂],^[2] Scheme 1)—has been worked out and the molecular structure of **1** has been determined.^[3]



Scheme 1. Synthesis of 1,1'-di(azido)ferrocene; tmeda = tetramethylethylenediamine.

According to the crystal structure analysis of **1**, the lattice contains two (ecliptic) rotamers, that is the 1,1' and the 1,2' isomer.^[3] The diamine **1** can be protonated, or oxidized (at the iron atom; Scheme 2) to give a green, paramagnetic cation **1a**

[*] Prof. Dr. M. Herberhold
Laboratorium für Anorganische Chemie
der Universität Bayreuth
Universitätsstrasse 30, 95440 Bayreuth (Germany)
Fax: (+49) 921-55-2540
E-mail: max.herberhold@uni-bayreuth.de

($\mu_{\text{eff}} = 2.1 \mu_{\text{B}}$), of which salts of the type [fc(NH₂)₂]⁺A[−] (anion A[−] = PF₆[−], OTf[−] or TCNE[−] (TCNE = tetracyanoethylene) were obtained.^[3]

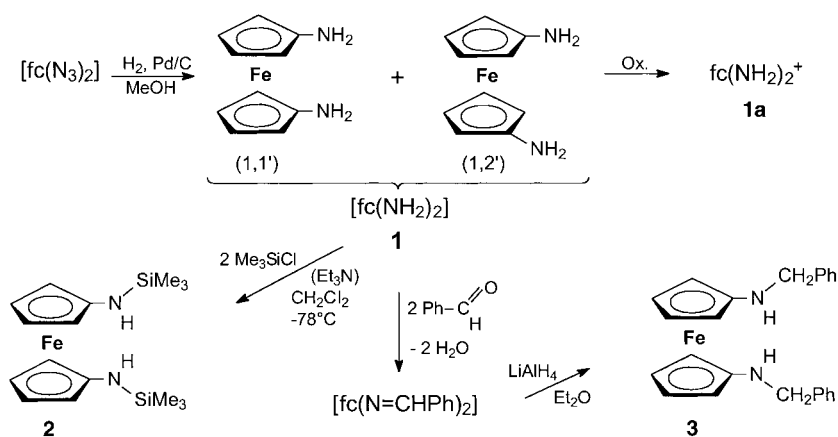
Starting from the primary diamine **1**, the silylated derivative [fc(NH-SiMe₃)₂] (**2**) can be prepared,^[5] while condensation with benzaldehyde and subsequent hydrogenation generates 1,1'-di(benzylamino)ferrocene, [fc(NH-CH₂Ph)₂] (**3**).^[6]

Titanium and Zirconium Complexes

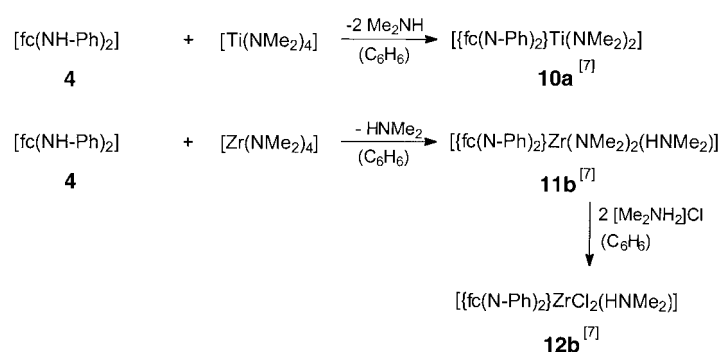
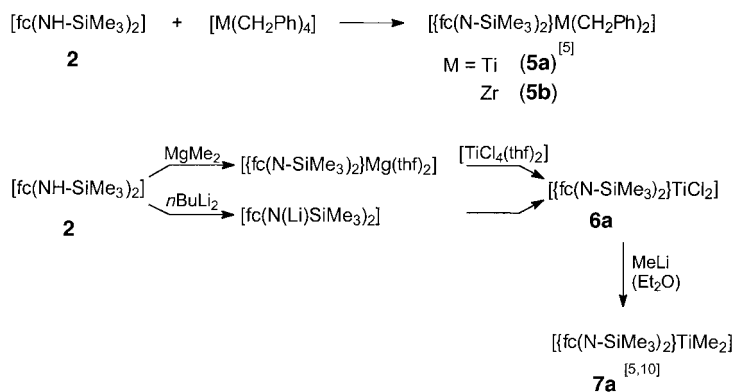
With regard to the development of new catalysts for the olefin polymerization, during the last few years an increasing number of complexes of the electron-poor transition metals titanium and zirconium with di(amido) chelate ligands has been investigated^[5–8] instead of the highly reactive di(cyclopentadienyl)titanium and -zirconium complexes (“metallocene catalysts”). The doubly deprotonated derivatives of the secondary diamines **2–4** serve as examples for 1,1'-ferrocenedi(amido) ligands (Scheme 2 and 5).

The use of amino-functionalized 1,1'-ferrocenedi(amido) sandwich compounds as chelate ligands provides two particular advantages:

- 1) Owing to the rotational mobility of the two cyclopentadienyl rings around the axis which is defined by the ring centers and the iron atom, the bidentate 1,1'-ferrocenedi(amido) ligand can easily adapt to the steric situation in the coordination sphere of the central metal,—as known for [fc(PPh₂)₂].^[4b]
- 2) Owing to the relatively high charge density in the electron-rich ferrocene sandwich, the iron center can be readily oxidized which may also be controlled by cyclovoltammetry.^[3, 7]

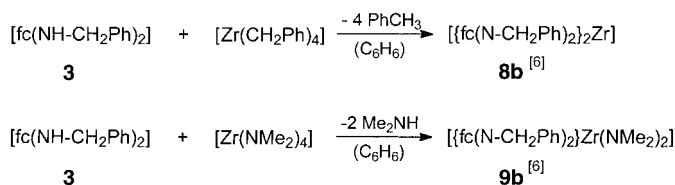
Scheme 2. Formation and reactivity of **1**.

The 1,1'-ferrocenedi(amido) complexes are formed either by aminolysis of tetrabenzyltitanium or -zirconium, respectively, or via metalated intermediates of the N-substituted 1,1'-di(amino)ferrocene (Scheme 3). Instead of the tetraben-

Scheme 5. Preparation of 1,1'-ferrocenedi(phenylamido) complexes of titanium and zirconium starting from the phenyl-substituted di(amido) ligand **4**.

Scheme 3. Preparation of 1,1'-ferrocenedi(trimethylsilylamido) complexes of titanium and zirconium.

zyl complexes $[M(CH_2Ph)_4]$ ($M = Ti, Zr$), tetrakis(dimethylamino) complexes $[M(NMe_2)_4]$ ($M = Ti, Zr$) can be subjected to aminolysis with **3** or **4** to give the corresponding di(amido) complexes (Scheme 4 and 5). In the case of the zirconium complexes containing 1,1'-ferrocenedi(phenylamido) ligands (Scheme 5), the Zr center behaves as a Lewis acid which eagerly adds dimethylamine.^[7]

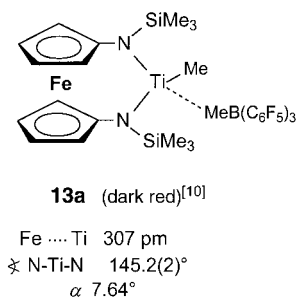
Scheme 4. Preparation of 1,1'-ferrocenedi(benzylamido) complexes of zirconium starting from the benzyl-substituted di(amido) ligand **3**.

The titanium and zirconium complexes **5–12** can be considered as 1,3-diaza-2-metalla[3]ferrocenophanes.^[4c] The crystal structure analyses (of **5b**, **6a**, **7a**^[5] and of **11b** and

12b^[7]) indicate that the two cyclopentadienyl rings always adopt a nearly eclipsed conformation, although the cyclopentadienyl ring planes slightly diverge at the di(amido)–metal bridge. The dihedral angle α between the ring planes lies in the range of 4–12°. In all complexes **5–12** the amidonitrogen atoms are coordinated in a trigonal-planar arrangement (sp^2 hybridization). Considering the distances between iron and zirconium center (333.9 pm in **11b**, 331.0 pm in **12b**), a direct interaction between the two metals can be excluded.

Complexes Containing Heterodimetal Interactions

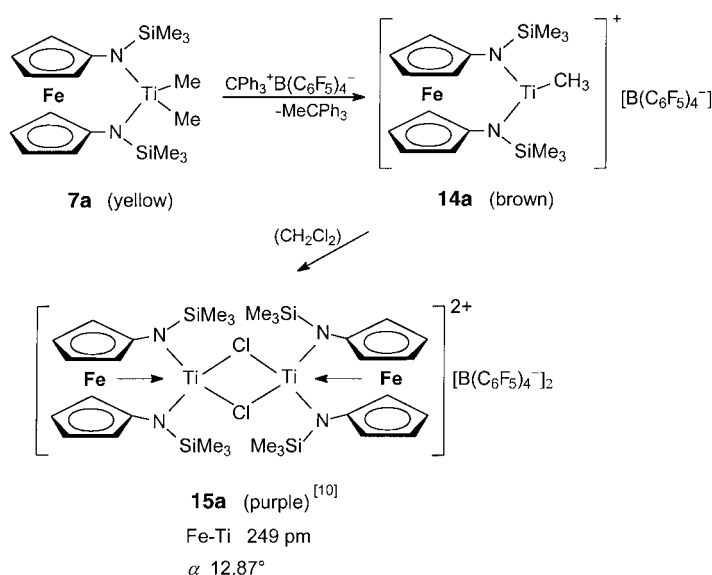
In Ziegler–Natta olefin polymerization processes, the catalyst must be activated by generation of a vacant coordination position at titanium or zirconium, respectively.^[9] As recently shown by Shafir and Arnold,^[10] this activation may be simulated by the reaction of **7a** with the strong Lewis acid $B(C_6F_5)_3$. In the resulting adduct **13a** one of the two methyl groups has been shifted towards boron with concomitant



formation of a pseudo-tetrahedral anion $[MeB(C_6F_5)_3]^-$; the distance from the titanium center to this methyl group (Ti–C 229.7(4) pm) is significantly longer than that to the remaining terminal methyl ligand (208.1(5) pm). Simultaneously, the Fe ... Ti distance in **13a** shortens to 307 pm.

Like $B(C_6F_5)_3$, the salt $[CPh_3][B(C_6F_5)_4]$ can be used to split off a methyl ligand from **7a**;^[10] the titanium cation thus

formed is stabilized by the 1,1'-ferrocenedi(amido) chelate ligand (Scheme 6). The cation in **14a**, which is coordinatively unsaturated at titanium, activates dichloromethane to generate the chloro-bridged dimer **15a**. The short Fe–Ti distance (249 pm) in **15a** can be ascribed to the formation of a dative



Scheme 6. Formation of a dative Fe → Ti bond in **15a**.

Fe → Ti bond. The sandwich structure is more distorted in **15a** than in **7a** and **13a**; the amido-nitrogen atoms in **15a** now possess trigonal-pyramidal coordination (sp^3), and the titanium center is no longer in the FeN_2 plane.

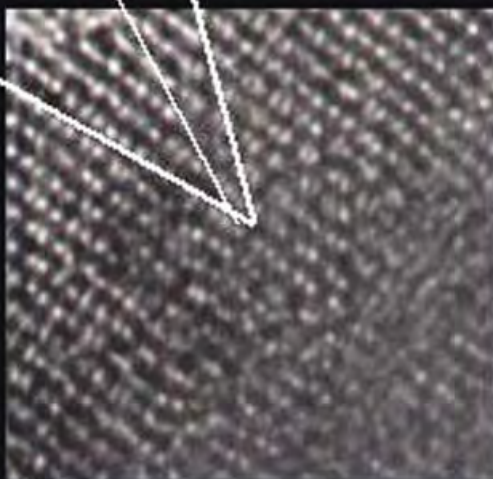
Experience has shown that it is difficult to extract the iron atom from the sandwich cage of the ferrocene and to force it into a dative bond to a metal (M) available in the vicinity, although its Lewis basicity is beyond doubt.^[4c, 10, 11] It is assumed that, as a prerequisite for a Fe → M heterodimetallic interaction, M has to be a Lewis-acidic, electron-poor center with a vacant coordination site. Some [3]ferrocenophanes such as $[\{\text{fcS}_2\}\text{M}(\text{PPh}_3)]$ (M = Pd (**16**),^[12] Pt (**17**)^[13]) and

corresponding cations^[11] like **18** and **19** fulfill these requirements, and the relatively short distance ($\text{Fe} \rightarrow \text{M} < 300 \text{ pm}$)—in addition to the distortion of the sandwich structure—is considered as an indication for a direct Fe–M interaction. Compound **15a** contains the shortest Fe–M bond (249 pm) observed so far in a ferrocene-containing heterodimetallic coordination compound. Evidently, the stabilization of cationic titanium centers by a 1,1'-ferrocenedi(amido) chelate ligand leads to the formation of a dative Fe → Ti bond.

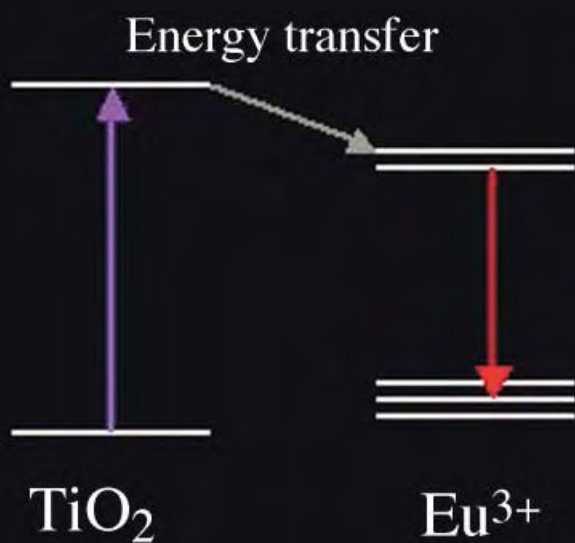
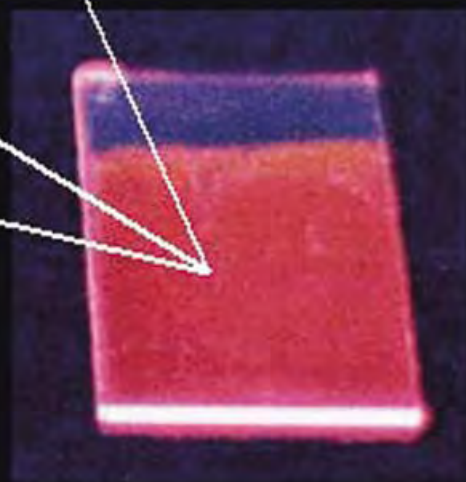
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Mesoporous titania, which is synthesized by using a one-step, sol–gel method has a wall structure composed of anatase nanocrystallites surrounded by regions of amorphous titania. It is possible to retain this unique structure with the inclusion of up to 8 mol% Eu^{3+} ions.



For more information see the following pages



Excitation of the anatase nanocrystallites within their band gap leads to nonradiative energy transfer to the europium ions, which exhibit a bright red luminescence. The titania nanocrystallites act as a sensitizer, since the f–f transitions in europium are parity forbidden. Since the europium ions sit at the crystalline–amorphous interface, concentration quenching of the europium emission is prevented.

Sensitized Luminescence of Trivalent Europium by Three-Dimensionally Arranged Anatase Nanocrystals in Mesostructured Titania Thin Films**

Karen L. Frindell, Michael H. Bartl, Alois Popitsch, and Galen D. Stucky*

In the last several years various routes have been developed to synthesize mesostructured titania powders^[1] and transparent titania thin films^[1a, 2, 3] with three-dimensionally arranged, nanometer-sized pores. The thin films developed in our group have a well ordered cubic array of mesopores and a wall structure composed of 1–5 nm anatase nanocrystallites embedded in an amorphous titania matrix.^[1a, 2] This interesting two-phase wall structure makes them a particularly attractive host matrix for optically active species such as trivalent rare earth metal (RE) ions. While the glasslike amorphous regions provide an ideal environment for the RE ions, the semiconducting nature of the anatase nanocrystallites can be used to sensitize the RE luminescence.^[4] Sensitization is an important process for technological applications of RE ions in photonic devices and color displays, since direct excitation of the parity-forbidden intra-f-shell RE metal ion crystal-field transitions is inefficient.^[5]

Here we report on a new luminescent material that combines a three-dimensional mesoscopically ordered array of nanocrystalline semiconductor particles with the nearly monochromatic emission of rare earth ions. We demonstrate that excitation of a cubic mesoporous titania thin film within its semiconductor band gap leads to bright narrow bandwidth emission from the europium activator ions by energy transfer from the semiconducting titania nanoparticle array, which acts as an effective antenna for the excitation light. Furthermore, we show that the unique two-phase composition of the mesopore walls allows high loading of Eu^{3+} ions without quenching their photoluminescence.

The europium-doped cubic mesoporous titania thin films were synthesized by a one-step sol–gel method, where trivalent europium ions were incorporated as the chloride salts into the mesopore walls (see Experimental Section). When the films are heat-treated, the chloride is removed and

the europium ions remain in the two-phase titania walls surrounded by an oxide environment. Due to a large mismatch in ionic radius between Eu^{3+} and Ti^{4+} (0.98 and 0.68 Å, respectively)^[6] the europium ions are not expected to occupy titanium sites within the anatase nanocrystallites, but rather to sit close to the grains in a glasslike environment.

Transmission electron micrographs (Figure 1) show that the titania films doped with up to 8 mol % Eu^{3+} have a cubic arrangement of pores, which are about 7–8 nm in size. This is

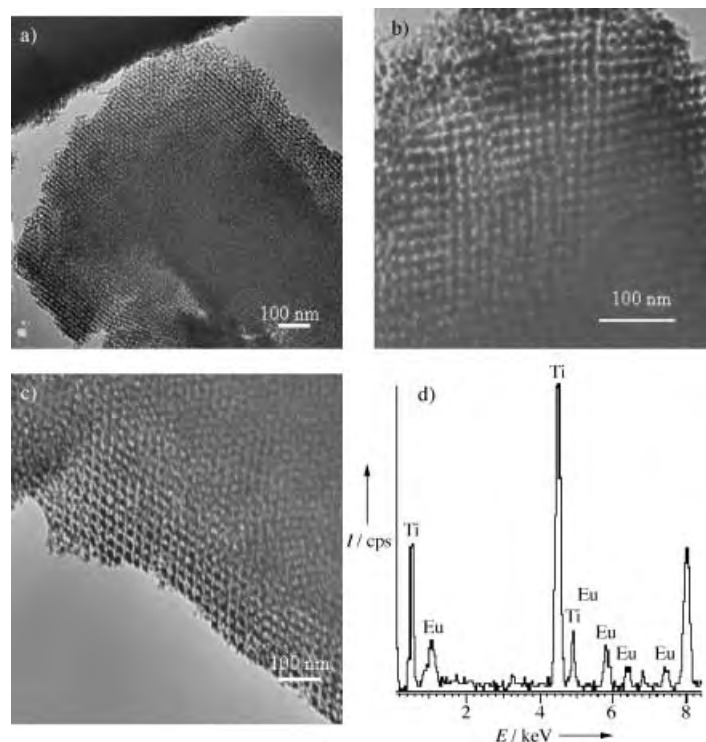


Figure 1. Transmission electron micrographs and EDX of Eu^{3+} -doped (8 mol %) cubic mesoporous titania thin films: a) View along the [100] zone axis, b) magnified view along the [100] zone axis, c) view down the [111] zone axis, d) EDX spectrum confirming the presence of europium in the mesopore walls. The measured europium content is 12 ± 4 mol %; this is an average value taken over several large areas.

in accordance with the undoped titania films and it is important to note that the incorporation of europium into the films does not destroy the mesostructure. Figure 1a and 1b show a view of the cubic structure of a Eu^{3+} -doped (8 mol %) titania film along the [100] zone axis, and Figure 1c shows a view along the [111] zone axis of the same sample. The high content of Eu^{3+} ions present in the walls of this sample is confirmed by energy dispersive X-ray spectroscopy (EDX) measurements (Figure 1d).

Figure 2 shows the UV/Vis absorption spectra of mesoporous titania films both undoped (spectrum a) and doped with 1 and 8 mol % Eu^{3+} (spectra b and c, respectively). In all three spectra a strong sharp increase in absorption corresponding to the titania semiconductor band gap appears at about 360 nm to 365 nm (3.45 to 3.40 eV). The shift in the band edges compared to that of bulk crystalline anatase, which has a band

[*] Prof. Dr. G. D. Stucky, K. L. Frindell,^[†] M. H. Bartl^[†]
Department of Chemistry and Biochemistry
University of California, Santa Barbara
Santa Barbara, CA 93106 (USA)
Fax: (+1) 805-893-4120
E-mail: stucky@chem.ucsb.edu
M. H. Bartl,^[†] Prof. Dr. A. Popitsch
Institute of Chemistry, Inorganic Chemistry
Karl-Franzens-University Graz, 8010 Graz (Austria)

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[†] These authors contributed equally to this work.

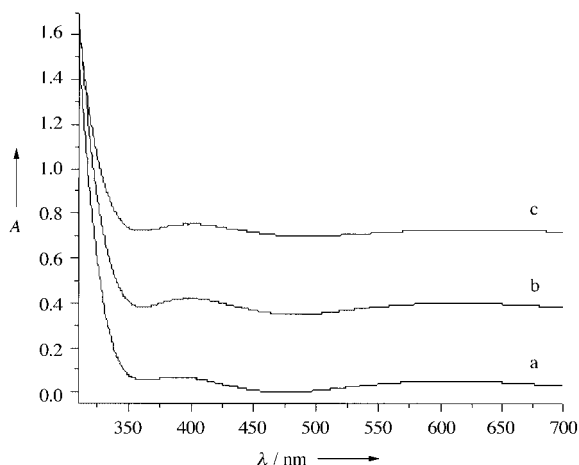


Figure 2. UV/Vis absorption spectra of undoped (spectrum a) and Eu^{3+} -doped (1 and 8 mol %; spectra b and c, respectively) cubic mesoporous titania thin films.

edge of about 380 nm (3.25 eV),^[7] is attributed to the small size of the anatase nanocrystallites (with radii between 0.5 and 2.5 nm) located in the amorphous titania walls.^[1a, 2] It is noteworthy that the position of the absorption band as well as the slope of the absorption band is the same for the undoped and doped films. Therefore it can be concluded that doping the films with europium ions does not significantly modify the nucleation and growth of the titania nanocrystallites. Importantly, no absorption peaks are observed arising from transitions within Eu^{3+} crystal-field states, which can be explained by the small thickness of the titania films in combination with the inherently low absorption cross sections of the parity-forbidden Eu^{3+} intra-f-shell crystal field transitions.^[5a] The broad absorption bands observed in the visible region are caused by interference colors that arise as a result of the thickness of the films.

Excitation of these films above the measured titania nanocrystallites band gap (360–365 nm) results in strong red light emission (Figure 3 and Figure 4). Although Eu^{3+} has no crystal field absorption transition at 330 nm,^[5a] emission bands between 550 and 720 nm, characteristic for Eu^{3+} , are present in the photoluminescence (PL) emission spectrum (Figure 4b). All of the five Eu^{3+} Russell–Saunders multiplets

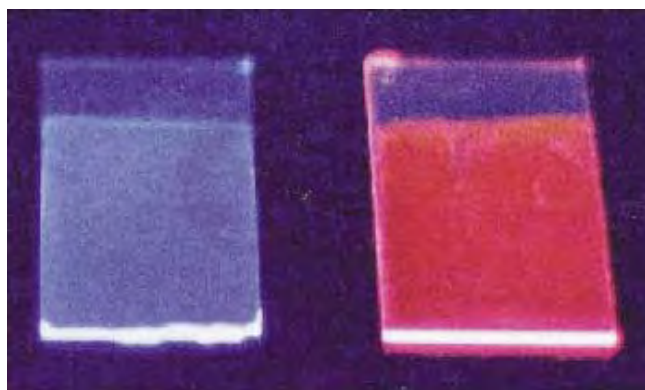


Figure 3. Color photograph of mesoporous silica (left) and titania (right) films, both doped with 8 mol % Eu^{3+} . The films are excited with a UV lamp at 300 nm.

$^5\text{D}_0 \rightarrow ^7\text{F}_J$ ($J=0, 1, 2, 3, 4$) show strong inhomogeneous broadening indicative of an amorphous oxide environment. A more detailed analysis of the most intense emission band, which is centered at 614 nm and corresponds to the $^5\text{D}_0 \rightarrow ^7\text{F}_2$ electric dipole transition, shows that this band is completely unresolved with a FWHM (full width at half maximum height) value of about 300 cm^{-1} —a value typically found for europium ions in an oxide glass environment.^[8] The PL excitation spectrum of the $^5\text{D}_0 \rightarrow ^7\text{F}_2$ emission band at 614 nm (Figure 4a) exhibits an intense broad peak starting at 360 nm and

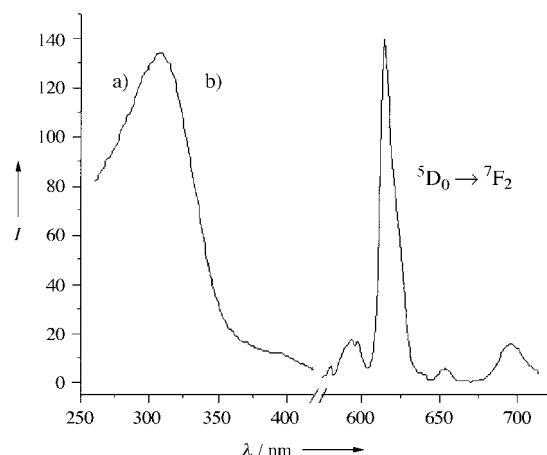


Figure 4. Photoluminescence excitation (spectrum a) and emission (spectrum b) spectra of a cubic mesoporous titania thin film doped with 8 mol % Eu^{3+} .

centered at around 310 nm. This peak coincides very well with the titania nanocrystallites absorption band edge (see Figure 2) indicating that the Eu^{3+} emission is associated with a nonradiative energy transfer process from the titania to the Eu^{3+} crystal field states.^[4] Moreover, we noticed that when the Eu^{3+} -doped films are excited below the titania band gap at 420 nm, no emission from europium ions is present. Instead, only a broad band between 600 and 750 nm is observed, which can be assigned to emission from titania defect centers.^[4, 9] To further prove that the Eu^{3+} emission is highly sensitized by titania, we prepared mesoporous silica thin films doped with the same Eu^{3+} concentration as in the titania films. Figure 3 shows a photograph of a silica film (left) and a titania film (right) both doped with 8 mol % Eu^{3+} ions and excited with a UV lamp at 300 nm. While strong red emission from the europium ions can be observed from the titania film, the silica film, which is unable to absorb at this wavelength shows no red Eu^{3+} emission. This was also confirmed by PL spectroscopy measurements.

To study the effects of concentration quenching of the Eu^{3+} luminescence, we determined the PL lifetime of the Eu^{3+} $^5\text{D}_0 \rightarrow ^7\text{F}_2$ emission band at 614 nm (see Experimental Section). A reasonable fit of the decay curves is achieved by using a biexponential function. The long-lived component obtained for each of our cubic mesoporous titania films with Eu^{3+} concentrations of 1, 3, 5, and 8 mol % has a PL lifetime of 550, 520, 470, and 500 μs , respectively. Additionally, in all the films a very short component with lifetimes of between 40 and 90 ns was detected. While the long component is typical for the

Eu^{3+} parity-forbidden intra-f-shell crystal-field transition $^5\text{D}_0 \rightarrow ^7\text{F}_2$, the short component is not attributed to Eu^{3+} , but to the very weak intrinsic background luminescence from the TiO_2 defect centers. Here it should be emphasized that no significant decrease in the PL lifetimes is observed when the Eu^{3+} content is increased. This indicates that even at europium concentrations as high as 8 mol % no quenching of the $\text{Eu}^{3+} ^5\text{D}_0 \rightarrow ^7\text{F}_2$ luminescence is present.

In summary, for the first time, a cubic mesostructured matrix of titania with a three-dimensional array of embedded anatase nanocrystals has been doped with high concentrations of europium ions. The semiconducting anatase nanocrystals sensitize the europium activator, which leads to an energy transfer system that produces a bright red, near-monochromatic luminescence. This work represents an interesting optical application of an all-inorganic mesoporous material. These have, because of their robust self-assembled framework, high surface area, simple processability, and air and moisture stability, potential to be incorporated into optical devices. The ability of the cubic mesostructured titania films to retain their structure and properties after the addition of a large amount of dopants opens the field to three-dimensionally ordered multicomposite materials for new electrical, magnetic, and optical applications.

Experimental Section

A typical trivalent europium ion doped, red photoluminescent film was prepared by dissolving $\text{EuCl}_3 \cdot 6\text{H}_2\text{O}$ (0.51 g) and Pluronic P123 (1 g) in absolute ethanol (12 g). This solution was added to a solution containing concentrated hydrochloric acid (2.7 mL) and titanium(IV) ethoxide (3.88 mL). After the solution had been aged, films were deposited on glass or quartz substrates by dip-coating at a rate of 1 mm s^{-1} . The films were heat-treated for 4 h at 400°C .

UV/Vis absorption spectra of these films were measured by using a Shimadzu UV-1610 recording spectrometer. The PL emission and excitation spectra were recorded with a Cary Eclipse PL spectrometer. For the PL lifetime measurements the films were excited with the 337 nm line of a pulsed (1 ns pulse width) nitrogen laser. The emission was dispersed by a monochromator and analyzed by using a digital oscilloscope.

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Multiple Emissions from 1,3-Diphenyl-5-pyrenyl-2-pyrazoline Nanoparticles: Evolution from Molecular to Nanoscale to Bulk Materials**

Hongbing Fu, B. H. Loo, Debao Xiao, Ruiming Xie, Xuehai Ji, Jiannian Yao,* Baowen Zhang, and Lianqi Zhang

The size dependence of organic crystals has not been as well investigated as that of inorganic crystals. The strong effects of confinement on electron–hole pairs in all three dimensions result in the size-tunable optoelectronic properties of semiconductor quantum dots,^[1,2] but are not expected in organic molecular crystals (OMCs), because of the small radius of the Frenkel exciton.^[3] The primary difference between inorganic and organic semiconductors is the bandwidth, or the degree of orbital overlap. In the case of OMCs, the electronic and optical properties are fundamentally different from those of inorganic semiconductors, because of weak van der Waals intermolecular forces.^[3,4] To date, the search for ways of controlling size, shape, and hence the properties of OMCs is still a challenge^[5–9], and an important aspect in the development of nanoscience.

Size effects may also be significant in OMCs.^[5,6] In our previous work, the size dependence of the optical properties of nanoparticles consisting of 1-phenyl-3-((*p*-dimethylamino)-styryl)-5-((*p*-dimethylamino)phenyl)-2-pyrazoline (PDDP) was shown to originate from charge-transfer (CT) exciton formation, with increasing nanoparticle size.^[10] Herein, the newly synthesized 1,3-diphenyl-5-pyrenyl-2-pyrazoline (DPP) is used as a model compound, in the light-emitting layer of an electroluminescent device, because of its strong, blue

[*] Prof. J. Yao, Dr. H. Fu, D. Xiao, R. Xie, X. Ji
Center for Molecular Science, Institute of Chemistry
Chinese Academy of Sciences
Beijing 100080 (P.R. China)
Fax: (+86) 10-64879375
E-mail: jnyao@ipc.ac.cn

Prof. B. H. Loo
Department of Chemistry
University of Alabama, Huntsville, AL 35899 (USA)
Prof. B. Zhang, Dr. L. Zhang
Technical Institute of Physics and Chemistry
Chinese Academy of Sciences, Beijing 100101 (P.R. China)

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pyrazoline fluorescence.^[11] DPP contains two chromophores, the pyrene and pyrazoline groups. The pyrene ring at the 5-position is almost perpendicular to the parent pyrazoline ring because of the large volume of the pyrene group, and thus their conjugated systems are separate from each other. It is interesting that a dilute solution of DPP in acetonitrile or tetrahydrofuran exhibits only the emission characteristics of the pyrene chromophore. In contrast, in the electroluminescent device, DPP shows only the emission characteristics of the pyrazoline chromophore.^[11] We found that DPP nanoparticles exhibit multiple emissions from both pyrene and pyrazoline groups and from a CT complex between pyrene and pyrazoline. The emission color of DPP nanoparticles is tunable between near-UV to green, by alteration of both the excitation wavelength and the nanoparticle size. For organic materials, luminescence applications and the multiple emissions of DPP nanoparticles are likely to be important in tailoring the properties of organic molecules to the resulting structures at nanoscale. In addition, the evolution of pyrene and pyrazoline emission in DPP nanoparticles caused by molecular aggregation and surface effects improves our understanding of the fundamental processes connecting OMCs.

DPP nanoparticles were prepared using a simple reprecipitation method.^[5, 10] In this process, a molecularly dispersed solution of DPP in a water-miscible solvent, acetonitrile, is mixed vigorously with an aqueous phase. Mixing the solvent and water phases changes the character of the solvent and induces the nucleation and growth of DPP nanoparticles. Figure 1 presents some field-emission scanning-electron

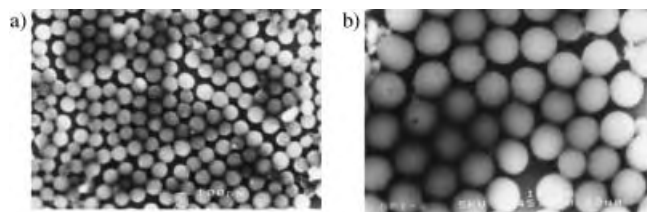


Figure 1. FESEM photographs of DPP nanoparticles with different sizes. a) 120 nm; b) 310 nm.

microscopy (FESEM) photographs of the DPP nanoparticles, in which the average nanoparticle sizes are 120 and 310 nm, respectively. These values agree roughly with those determined by dynamic light scattering (DLS), in which the polydispersity was less than 10%.^[12] It can be seen from Figure 1 that the narrow size distribution of DPP nanoparticles caused them to self-assemble into a two-dimensional array, in a way similar to that observed for many other colloidal particles.^[13] Measurements of the surface potential of these nanoparticles showed that they are negatively charged, and that the ξ -potential retained a value of about -32 mV with varying nanoparticle size.

Figure 2 displays the UV/Vis absorption spectra of DPP nanoparticles of different sizes, dispersed in water. Compared with the absorption spectrum of a 1,3-diphenyl-2-pyrazoline (DP) solution in ethanol, the spectrum of the dilute DPP in acetonitrile solution is apparently a combination of the

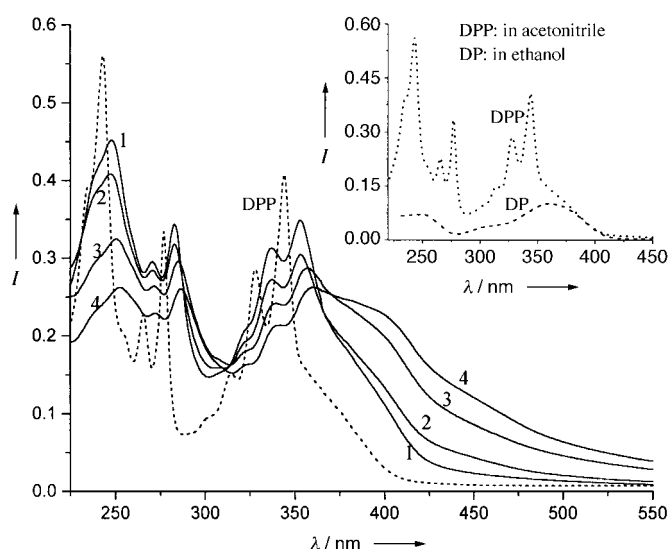


Figure 2. The UV/Vis spectrum of DPP nanoparticles of 1) NP1, 65 nm; 2) NP2, 120 nm; 3) NP3, 180 nm, and 4) NP4, 310 nm in aqueous dispersions. Inset: DPP in acetonitrile solution with a concentration of 1.0×10^{-5} mol L⁻¹, DP in ethanol solution with a concentration of 8.0×10^{-6} mol L⁻¹. I = relative intensity.

spectra of the pyrene and pyrazoline groups (inset in Figure 2). On going from spectrum 1 to 4, with increasing nanoparticle size, the absorption features of the pyrazoline chromophore become gradually more prominent in the region from 370 nm to 420 nm, while the absorption bands of pyrene shift to longer wavelengths. Moreover, a new feature gradually appears at about 450 nm.

The emission spectrum of the DPP in acetonitrile solution (Figure 3A) demonstrates the characteristics of the pyrene group monomer emission bands at 380–410 nm, and a structureless band at 520 nm assigned to a pyrene excimer.^[11] In contrast, the spectrum of DPP bulk crystals shows an emission band centered at 445 nm (see Figure 3F). The shape of the emission of the DPP bulk crystals is similar to that of DP bulk crystals. There are significant differences between the fluorescence features of nanoparticles and those of monomers and bulk crystals. Figure 3D (nanoparticle NP3) is typical of the fluorescence features of nanoparticles. The nanoparticle emission (black line) divides into three parts at 385, 465, and 570 nm. The red, yellow, and blue lines are the excitation spectra obtained by monitoring the emissions at 385, 465, and 570 nm, respectively. We found that the intensity of the different emission parts at different excitation wavelength, λ_{ex} , is proportional to the intensity at λ_{ex} in their corresponding excitation spectra. For example, when λ_{ex} is fixed at 290 nm, the first part of the emission vanishes, while the second and third parts are still observed and the second part becomes the strongest. The multiple emissions have different individual optical channels, and can be tuned easily by the selection of λ_{ex} .

Figure 4 shows the proposed emission transitions for DPP in monomers, nanoparticles, and bulk crystals, based on the above spectroscopic study as well as on the fluorescence decay times given in Table 1. For DPP, the first part of the nanoparticle emission at 380–410 nm apparently arises from the pyrene group. Through comparison with the emission

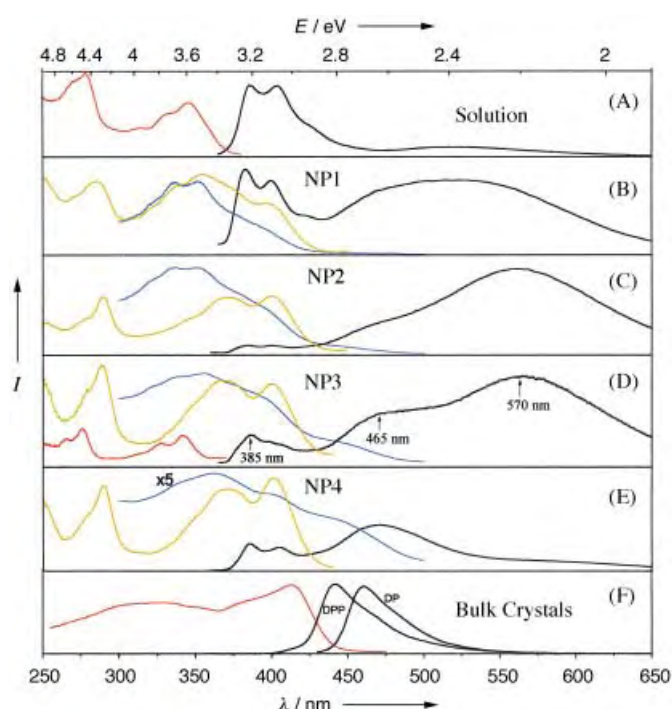


Figure 3. The fluorescence excitation and emission spectra of A) DPP in acetonitrile with a concentration of $1.0 \times 10^{-5} \text{ mol L}^{-1}$; and nanoparticles of B) NP1, C) NP2, D) NP3 and E) NP4; F) DPP and DP bulk crystals. The colored lines are the excitation spectra obtained by monitoring the emission at 385 (red), 465 (yellow), and 570 nm (blue), except for the red line in E, which was obtained by monitoring the emission at 445 nm. Black lines are emission spectra obtained by excitation at 345 nm. I = relative intensity.

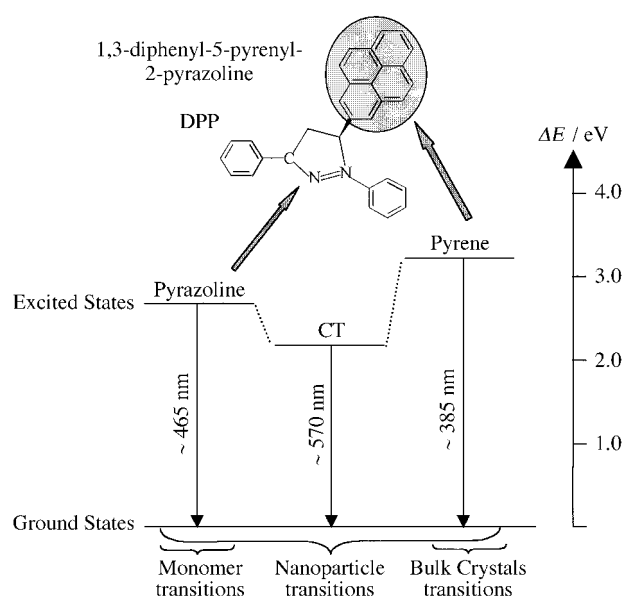


Figure 4. The emission transitions for DPP in monomers, nanoparticles, and bulk crystals.

characteristics of DP in ethanol solution, the nanoparticle emission at 465 nm is attributed to the pyrazoline group. It must be noted that the band at 400 nm in the corresponding excitation spectra (yellow lines) is not observed in the excitation spectrum of DP in ethanol solution, monitored at 460 nm. Whereas, for the PDDP nanoparticles^[10] this band as well as that at 370 nm can be assigned to the charge-transfer

Table 1. The fluorescence decay times of different samples at room temperature.

Sample	Excitation wavelength [nm]	Monitored wavelength [nm]	Decay times [ns]
DPP nanoparticles	345	385	38.2 ± 0.42
		465	3.76 ± 0.30
		560	9.20 ± 0.33
DP in ethanol solution	360	460	4.23 ± 0.30
		345	–, 8 ^[b]
pyrene crystal ^[a]	345	395	–, 8 ^[b]
		465	70, 180 ^[b]

[a] From reference [13]. [b] Measured at 77 K.

state between pyrazoline groups and the pyrazoline ring π – π^* transition. The nanoparticle emission at 465 nm originates from aggregate states, which explains why the emission is not quenched by water. In contrast, the emission from the pyrazoline ring, caused by the twisted intramolecular charge transfer from the N-1 atom to the C-3 atom in the DPP in acetonitrile solution, is quenched by acetonitrile.^[14, 15] The third band of the emission is unlikely to originate from the pyrene excimer, in which the emission wavelength is at 465 nm and the fluorescence lifetime is 70 ns at 298 K in pyrene crystals.^[16] It can be seen that the excitation spectrum (Figure 3) corresponding to the third emission band (blue line) is similar to the corresponding absorption spectrum for each nanoparticle (NP1–NP4) shown in Figure 2, and includes the energy levels of both pyrene and pyrazoline groups. Therefore, we assigned it to an aggregated state of a charge-transfer complex between pyrene and pyrazoline groups. The broad features of the excitation spectrum are also indicative of a CT state.^[17] Moreover, the gradually appearing feature at 450 nm in the absorption or excitation spectra (blue line in Figure 3), with increasing nanoparticle size, may originate directly from the energy level of the pyrene–pyrazoline CT states, since the 570 nm emission was observed by excitation using 450 nm light. The three nanoparticle emission bands at 385, 465, and 570 nm originate from the pyrene and pyrazoline groups and from a CT complex between the pyrene and pyrazoline groups, respectively.

The evolution of the multiple emissions of DPP nanoparticles is also studied as a function of nanoparticle size (Figure 3B–E). Compared with the spectra of the monomers shown in Figure 3A, molecular aggregation effects begin to influence the properties of DPP molecules in NP1. The greater intensity of the pyrene emission in Figure 3B than in Figure 3C–E indicates that individual molecules also play an important role in the properties of nanoparticles of this size, as do molecular aggregates. As the nanoparticle size increases, the emission at 570 nm is strongest in Figure 3c and then gradually decreases from Figure 3c to 3e. The orientation of the building units is identical because atoms can be regarded as hard spheres. However, the spatial configuration of organic molecules in organic nanoparticles plays an important role in their resulting properties. For example, the formation of intermolecular charge-transfer complexes demands that the donor–acceptor pair is in an approximately face-to-face arrangement, to give the largest orbital overlap.^[4] Initially, when DPP molecules aggregate to form nanoparticles, two kinds of molecular aggregation, pyrazoline–pyrazoline

(Py–Py) and pyrene–pyrazoline (Pr–Py) pairs, randomly begin to form nanoparticles such as those in NP1, which cause the emissions from them to overlap to some extent (Figure 3). As DPP nanoparticles grow further, as is the case for NP2(>100 nm), the enhanced Coulombic interaction energies between molecules^[5] cause the Pr–Py pairs to form mainly on the surface of the nanoparticles, because of the larger volume of Pr–Py than Py–Py. This hypothesis explains why the emission from Pr–Py CT states at 570 nm is most intense in NP2 and then gradually decreases from NP2 to NP4 (Figure 3); as a result of the decrease of the surface-to-volume ratio from NP2 to NP4. When the nanoparticle size increases further into the bulk phase, the Py–Py pair plays a dominant role in the properties of bulk crystals, and only pyrazoline-like emission is observed. The absence of pyrene monomeric emission in DPP bulk crystals may be a result of a low fluorescence quantum yield in bulk crystals as exhibited by the pyrene bulk crystals (as shown in Figure 3).^[16] Therefore, the multiple emission of DPP nanoparticles and their evolution as a function of size is caused by the molecular aggregation and surface effects.

In summary, unlike the corresponding monomers and bulk crystals, DPP nanoparticles were found to exhibit a special type of multiple emission, which ranges from near-UV to green, and as a result of the surface effects, is tunable by alteration of both the excitation wavelength and nanoparticle size. This novel phenomenon is of interest in the tailoring of the properties of optical materials. Thus, organic crystals also possess significant size effects like those of inorganic semiconductors and metals, but with a greater diversity because of a wide variety of organic molecular structures.

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Template Effects, Asymmetry, and Twinning in Helical Inclusion Compounds**

Mark D. Hollingsworth,* Michael E. Brown, Michael Dudley, Hua Chung, Matthew L. Peterson, and Andrew C. Hillier

Dedicated to Professor J. Michael McBride

Of the achiral substances in our world, only a small fraction are spontaneously resolved into enantiomorphous crystals that can be separated. Spontaneous resolution may occur when the molecular constituents of the crystal adopt chiral or skewed conformations or when molecules adopt chiral arrangements, such as a helices, which act as templates for further growth of the given enantiomorph. Certain inclusion compounds (such as those derived from urea and tri-*o*-thymotide) have received attention because spontaneous resolution of the inclusion compound leads to chiral discrimination between guest enantiomers.^[1, 2] For urea inclusion compounds (UICs), in which urea forms helical channels in the presence of long-chain guests,^[3] the literature has uniformly treated these materials as either right- or left-handed homochiral objects. In part, this misconception occurs because the typical needle morphology makes it difficult to observe the presence of enantiomorphous domains. Through the combined use of optical microscopy, synchrotron white beam X-ray topography (SWBXT), and crystallography, we demonstrate here the existence of two types of previously unrecognized macroscopic twinning in UICs. This work provides further support for our models of crystal growth^[4] and hydrogen-bond topologies in UICs containing bis(methyl ketone)s^[5] and provides a rationale for chiral (Brasil) twinning in these materials. This rationale may serve as a model for chiral twinning in other helical materials,^[6] especially those with double helices.

Most urea inclusion compounds consist of well-defined host structures in which urea molecules are hydrogen-bonded to form honeycomb networks of nonintersecting hexagonal channels. Within these channels, long-chain guest molecules

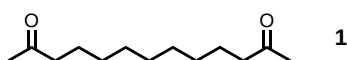
[*] Prof. M. D. Hollingsworth, M. E. Brown, Dr. M. L. Peterson
Chemistry Department
Kansas State University
111 Willard Hall, Manhattan, KS 66506 (USA)
Fax: (+1) 785-532-6666
E-mail: mdholl@ksu.edu

Prof. M. Dudley, Dr. H. Chung
Department of Materials Science and Engineering
State University of New York at Stony Brook
Stony Brook, NY 11794 (USA)

Prof. A. C. Hillier
Department of Chemical Engineering
University of Virginia
Charlottesville, VA 22904 (USA)

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pack within van der Waals contact. Although UICs typically form high-symmetry, incommensurate (nonstoichiometric) structures,^[7] we have identified a series of commensurate UICs containing homologous bis(methyl ketone)s.^[3–5, 8] For such guests and their congeners, a reliable host–guest hydrogen-bonding motif can be used to control both internal symmetry and external shape of these crystals. In most bis(methyl ketone)/urea crystals that we have studied, urea molecules turn about their twofold axes to form hydrogen bonds with guest molecules in adjacent channels. Using this motif, we have developed a simple geometric model that allows us to use the host:guest stoichiometry, natural length of the guest, and the parity (odd or even) of the guest molecule's chain to restrict the possible host–guest hydrogen-bonding topologies. In the case of 2,12-tridecanedione/urea (**1**/urea), our prediction of the correct polymorphic structure was instrumental in our structure solution and refinement from the X-ray data.



A description of helical wheels is given elsewhere,^[5] so only the salient features are presented here. Most UICs are chiral objects in which the two intertwined helices are of the same handedness and are related by C_2 axes perpendicular to the channel. Each urea molecule in helix 1 (numbered 1, 2, and so on as one moves down the channel) has a counterpart directly across the channel (at the same z coordinate) in helix 2 (numbered 1', 2', and so on). These pairs of molecules (for example, 1 and 1') lie parallel to each other. If the host:guest stoichiometry is known (or can be predicted), it is a simple matter to write down the relative positions of the urea molecules that are in position to use their *syn* N–H groups to form hydrogen bonds with the guest. For **1**/urea, the natural length of the guest (18.8 Å)^[3, 4, 9] predicts a host:guest stoichiometry of 10:1, so the hydrogen-bonding motif requires that the two C=O groups of a given guest molecule are tethered to urea molecules in the first and eleventh positions in the channel (since half of a urea molecule is used at each end of the guest). The helical-wheel diagram shown in Figure 1 represents four possible combinations of host–guest connectivities (1–11, 1–11', 1'–11, 1'–11'), the first and fourth of which are degenerate. Long arrows in the center of each diagram denote the orientations of the two carbonyl groups in one guest molecule and give a rough idea of the dihedral angle between them.

For this odd-chain guest, whose natural length is slightly longer than the commensurate repeat of 18.36 Å, Figure 1B predicts that a stable structure (with low torsional strain) can be formed. Indeed, the channel axis oscillation photograph indicates a commensurate structure with $3c'_g = 5c'_h$ (urea: guest = 10:1), and the crystals grow as thin {001} plates, as predicted for a commensurate structure in which guests are tethered to the host and offset from guests in adjacent channels by 0 Å.^[4] Further support for this structural motif came from atomic force microscopy (AFM), which showed that terraces on the {001} faces are molecularly smooth and offset

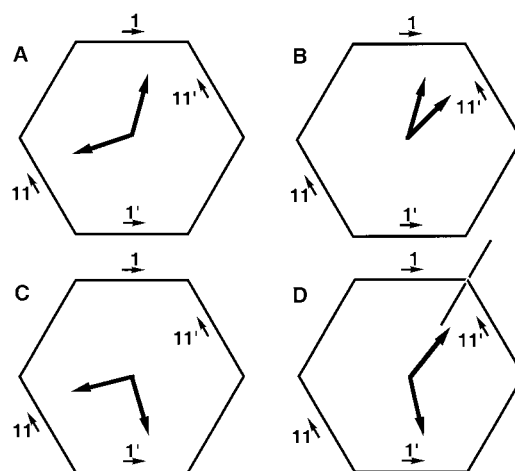


Figure 1. Right-handed helical-wheel diagram showing four possible arrangements for host–guest hydrogen bonding in **1**/urea. (An equivalent diagram can be drawn for a left-handed helix.) The numbered arrows around the periphery of the hexagon refer to the orientations of urea C=O groups. The C_2 axis shared by A and D (which are degenerate) is shown in D. For this odd-chain guest, this simple model correctly predicts topology B (see Figure 4e).

along c by integral multiples of the guest length, with average height of 18.1(5) Å or a multiple thereof (Figure 2). Nevertheless, our early attempts to solve the structure from area detector data proved unsuccessful because of disorder of the guest.

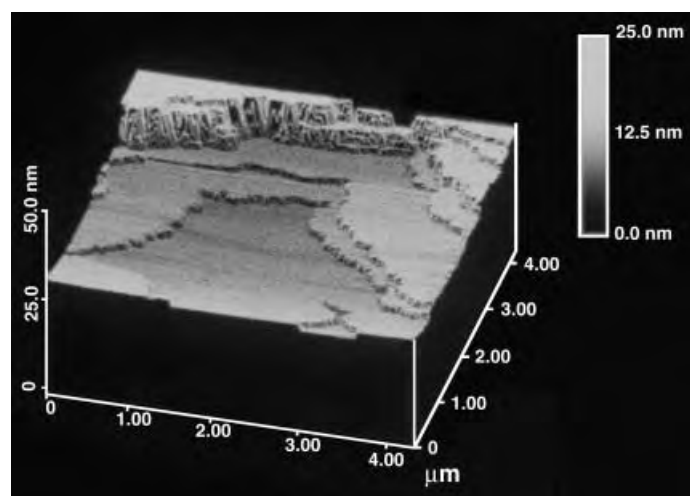


Figure 2. AFM images of the {001} face of **1**/urea recorded in air on a Digital Nanoscope III instrument in tapping mode. The average step height for six different ledges was 18.1(5) Å or a multiple thereof.

For a commensurate structure of **1**/urea with $3c'_g = 5c'_h$ one predicts that guests will be related by threefold (3_1) screw axes along the channels and that the crystals will therefore have uniaxial optical properties (that is, with no ferroelastic distortion in the ab plane).^[8] Photomicrographs can therefore reveal optical activity, which for most UICs is relatively insensitive to guest identity in the visible region of the spectrum.^[2b] Because there were no previous reports of chiral twinning in UICs, we were surprised to find that in **1**/urea and related materials (2-tridecanone/urea, 2,9-decanedione/

urea,^[4] and mixed UICs of 2-undecanone and 6-undecanone), both dextrorotatory and levorotatory domains could be observed (Figure 3a and b). The twin boundaries that separate these domains occur every 60° and are coincident with the {110} faces of the crystal.

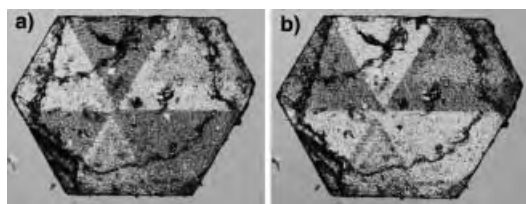


Figure 3. a) Photomicrograph of **1**/urea (0.26 mm thick) with polarized light at 546 nm and the analyzer rotated by +9° from the crossed position (dark = dextrorotatory). b) The same crystal with the analyzer rotated by −9° from the crossed position (dark = levorotatory). In each, the view is down the channel axis.

Because the nature of the twin boundaries in UICs was important for our studies of domain switching in ferroelastic UICs^[8] (whose birefringence would mask any chiral twinning), we subjected this crystal to SWBXT at beamline X-19C at the National Synchrotron Light Source. In this technique, the highly collimated white beam provides topographic images with high spatial resolution for each Bragg reflection.^[10] The positions and intensities of the resulting images are sensitive to twinning, strain, dislocations, and differences in structure factors for reflections in different domains.^[11] After an exposure of 10–15 s, one obtains a Laue image corresponding to the most intense reflections in the diffraction pattern (Figure 4a). For **1**/urea, reflections occur in three separate sets, one of which shows no contrast. The other two sets form complementary images (labeled **d** and **e**) that reveal sectoring in addition to the chiral twinning described above (Figure 4b and c) and little or no apparent strain at any of the domain boundaries.

In anticipation of a trigonal structure, we indexed the topograph with a nonprimitive, rhombohedral cell ($a = 55.96 \text{ \AA}$, $\alpha = 14.63^\circ$),^[12] and found that in the **d** and **e** reflections, the contrast pattern obeyed the conditions for obverse and reverse settings of a rhombohedral cell ($-h + k + l = 3n$ and $h - k + l = 3n$). These unit cells are related by 180° (or equivalent 60°) rotation about the channel axis.^[13] Although this rotational (Dauphiné) twinning^[14] was invisible under the microscope, the X-ray topograph could be used as a guide for cleavage of this crystal into eleven fragments. Two complementary fragments [fragment 7-(+)-**e** (dextrorotatory type **e**) and fragment 2-(-)-**d** (levorotatory type **d**)] were used for X-ray data collection at −75 °C (see arrows in Figure 4b and c).

Structure solution and refinement revealed that the apparent rhombohedral symmetry was only approximate, and that the structures could be solved in the trigonal space groups $P3_112$ and $P3_212$. Because there are no heavy atoms in these structures, the absolute structures could not be determined unambiguously with either Flack or Bijvoet methods,^[15] but the favored assignments (Figure 4d and e) agree with Schlenk's model-based correlation of positive optical rotation

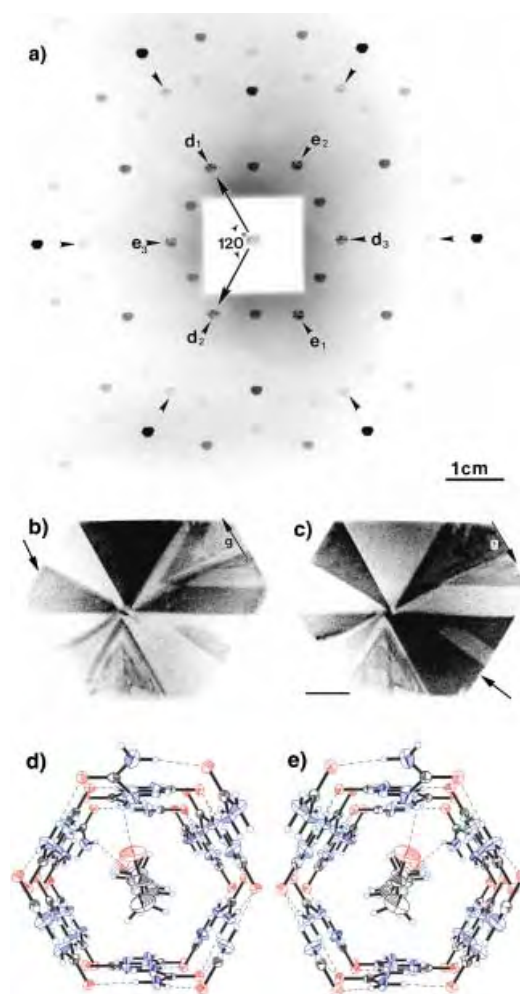


Figure 4. a) SWBXT Laue image of **1**/urea held with its {001} face perpendicular to the X-ray beam. Note complementary contrast in reflections labeled **d** and **e**. b) SWBXT of **d**₁ reflection for **1**/urea (**g** vector shown in upper right). Arrow on left denotes levorotatory region (2-(-)-**d**) used for X-ray crystal structure shown in Figure 4d (see text). c) SWBXT of **e**₁ reflection for **1**/urea (**g** vector shown in upper right). Arrow on right denotes dextrorotatory region (7-(+)-**e**) used for X-ray crystal structure shown in Figure 4e. Scale bar: 400 μm. d) and e) ORTEP diagrams (30% ellipsoids) showing $P3_112$ crystal structure of levorotatory fragment shown in Figure 4b (d) and $P3_212$ crystal structure of dextrorotatory fragment shown in Figure 4c (e). The absolute configurations are not proven.

with the right-handed (3_1) sense of the urea helix.^[2b] Nevertheless, the structures^[16] confirm that in the presence of host–guest hydrogen bonding, the helical-wheel method correctly predicts the observed polymorph (cf. Figures 1B and 4e).

Facet indexing and correlation with the overall crystal morphology showed that the **d** and **e** domains are related to each other by 60° rotation about the channel axis. (For fragment 2-(-)-**d**, which was contaminated by a small amount of the adjacent type **e** domain, the largest peak in the difference Fourier map assumed the position of an oxygen atom in a guest carbonyl group rotated 58° about the channel axis.) This macroscopic rotational twinning is established during crystal growth, persists over a period of years, and is remarkable given the dynamic nature of guests in other UICs^[17] and the lack of ferroelastic distortion in **1**/urea. (SWBXT of the upper right third of this crystal, which was

held between -20 and 20°C for two years after the initial topograph, showed no noticeable degradation in the Dauphiné twin boundaries.)

Although chiral twinning is counterintuitive in a strongly hydrogen-bonded helical system, in which templated growth predominates, clues to the twinning mechanism in **1**/urea come from our recent structures of a series of centrosymmetric UICs.^[18] For $\text{Br}(\text{CH}_2)_6\text{Br}/\text{urea}$ and congeners (space group $P2_1/n$, b unique), the n -glide provides a convenient mechanism by which the structures on either side of certain (001)-type channel walls are related by mirror symmetry. In $\text{Br}(\text{CH}_2)_6\text{Br}/\text{urea}$, the n -glide generates a looplike topology of hydrogen bonds in which certain rows of urea molecules lying closest to the (001) plane are translated along the channel relative to their counterparts in helical structures. From a diagram based on our helical-wheel formalism, it is possible to show that the loop topology in $\text{Br}(\text{CH}_2)_6\text{Br}/\text{urea}$ can serve as a template for the formation of enantiomorphic helices above and below the (001) plane (Figure 5). (No other primitive planes in the $\text{Br}(\text{CH}_2)_6\text{Br}/\text{urea}$ structure can directly template

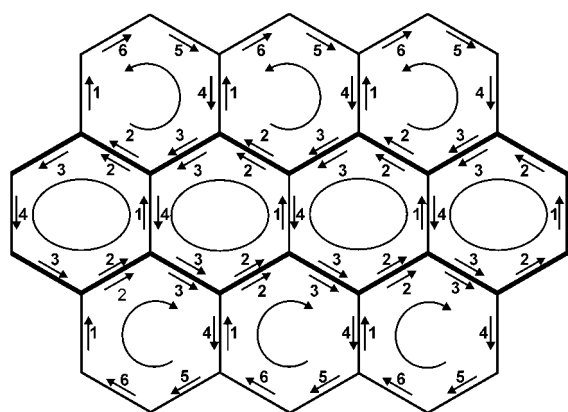


Figure 5. Modified helical-wheel diagram showing how the stacked loop structure of a centrosymmetric UIC (such as $\text{Br}(\text{CH}_2)_6\text{Br}/\text{urea}$) can serve as a template for the formation of left- and right-handed helices above and below the (001) plane. Arrows in the middle row of channels correspond to C=O axes for urea molecules in the $P2_1/n$ structure found in numerous $\text{X}(\text{CH}_2)_6\text{X}/\text{urea}$ inclusion compounds. The numbers correspond to the relative positions along the channel axis of those urea molecules. At the bottom of this centrosymmetric row, urea molecules 2 and 3 template the formation of a right-handed helix, in which the sequence 1, 2, 3, 4, 5, 6 leads in a clockwise sense away from the observer (down the channel). At the top, urea molecules 2 and 3 template the formation of a left-handed helix (counterclockwise from 1 through 6). These right- and left-handed helices correspond to the unprimed and primed helices described above in the helical-wheel formalism.

both right- and left-handed helices.) Although the precise structure of the chiral twin boundaries is not available from SWBXT of **1**/urea, support for this twinning mechanism comes from the structural correspondence between the {001} planes in $\text{Br}(\text{CH}_2)_6\text{Br}/\text{urea}$ and the {110} planes of **1**/urea, which exhibit chiral twinning.^[18]

Although **1**/urea is not ferroelastic, these results illuminate our studies of domain switching in ferroelastic crystals such as 2,10-undecanedione/urea, in which domain reorientation occurs under applied external anisotropic stress.^[8] Because the present work shows that chiral twinning may occur in

helical urea systems, and that the most likely topology at this type of domain boundary is nonhelical, we anticipate that ferroelastic UICs containing such twin boundaries will have high barriers to domain wall motion.^[19] With the recent emergence of optical techniques for measuring chirality in biaxial crystals,^[20] identification of Brasil-type domain walls may soon be possible.

Experimental Section

1/urea: A solution of 2,12-tridecanedione (0.301 g, 1.42 mmol, prepared by literature methods^[21]), urea (0.857 g, 14.3 mmol, Baker AR) and MeOH (7.0 mL, Mallinckrodt) was allowed to evaporate at RT. After one day, thin plates (0.331 g) were collected. M.p. $134.5-135^{\circ}\text{C}$, uncorrected; ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 5.41$ (s, urea), 2.38 (t, $^3J(\text{H,H}) = 7.4$ Hz), 2.04 (s), 1.41 (m), 1.20 (m), urea:guest (10.3:1); IR (Nujol): $\tilde{\nu} = 1717\text{ cm}^{-1}$.

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Structural Analysis of C₆₀ Trimers by Direct Observation with Scanning Tunneling Microscopy **

Masashi Kunitake,* Shinobu Uemura, Osamu Ito, Koichi Fujiwara, Yasujiro Murata, and Koichi Komatsu*

All-carbon fullerene oligomers and polymers have attracted considerable interest from a wide range of scientific and technological view points.^[1] The formation, structure, and characteristics of fullerene oligomers, such as dimers and

trimers, and fullerene polymers are of particular interest because of their potential usefulness as molecular devices, and in the fields of optoelectronics and nanotechnology. These materials have been prepared under photochemical^[2] or high-pressure/high-temperature conditions,^[3] or by the action of alkali metals upon fullerenes.^[4] Recently, it was found that the solid-state mechanochemical reaction of C₆₀ with potassium salts such as KCN, KOAc, and K₂CO₃, with highly reducing metals, or with solid aromatic amines under “high-speed vibration milling (HSVM)” conditions, can successfully produce the fullerene dimer, C₁₂₀.^[5, 6] Furthermore, the trimers (C₁₈₀), which include a variety of structural isomers, were also found to be formed by this reaction.^[7]

When C₆₀ was treated with 4-aminopyridine under HSVM conditions, analysis of the reaction mixture with high-pressure liquid chromatography (HPLC) using a Cosmosil 5PBB column and eluting with *o*-dichlorobenzene (*o*-DCB) showed two small peaks (fractions A and B) corresponding to the trimer (C₁₈₀). These peaks appeared after the major peaks for C₆₀ and the dimer (C₁₂₀). Upon evaporation of the solvent, the material giving rise to the C₁₈₀ peaks amounted to 4 % yield based on C₆₀. Further analysis and separation using different HPLC conditions with a Cosmosil Buckyprep column and eluting with toluene revealed that fraction A consisted of at least three isomers (A1, A2,^[16] and A3), while fraction B was a single component (Figure 1). The identity of C₁₈₀ was estab-

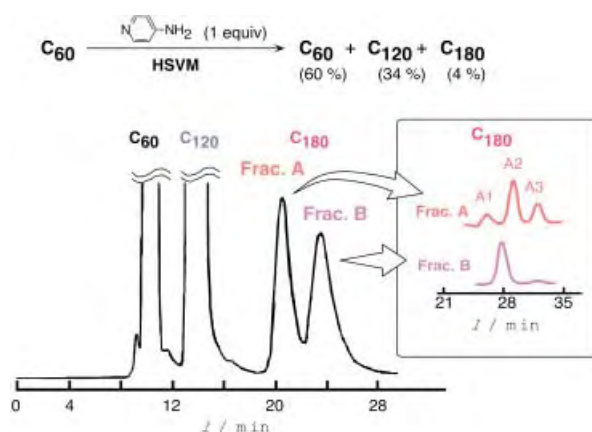


Figure 1. Elution traces for HPLC separation of C₁₈₀ isomers, with UV detection at 326 nm. Left: Cosmosil 5PBB column eluting with *o*-DCB, and right (inset): Cosmosil Buckyprep column eluting with toluene.

lished by solution-phase cyanation and observation of the peak arising from the C₁₈₀(CN)[–] ion by atmospheric pressure chemical ionization (APCI) mass spectral analysis (negative ion mode). APCI mass analysis of the C₁₈₀ itself exhibited only the fragment peak of C₆₀.^[7]

Unfortunately, the extremely low solubility of C₁₈₀ in ordinary solvents did not allow the chemical structure to be determined by ¹³C NMR spectroscopy. Such low solubility also made it difficult to prepare single-crystal samples of C₁₈₀ for X-ray diffraction analysis. In the present study, however, we successfully achieved structural identifications of the C₁₈₀ isomers by direct visualization using scanning tunneling microscopy (STM).

[*] Prof. Dr. M. Kunitake, Dr. S. Uemura
Department of Applied Chemistry & Biochemistry
Faculty of Engineering, Kumamoto University
Kurokami, Kumamoto 860-8555 (Japan)
Fax: (+81)96-342-3673
E-mail: kunitake@chem.kumamoto-u.ac.jp

Prof. Dr. K. Komatsu, K. Fujiwara, Dr. Y. Murata
Institute for Chemical Research
Kyoto University
Uji, Kyoto 611-0011 (Japan)
Fax: (+81)774-38-3178
E-mail: komatsu@scl.kyoto-u.ac.jp

Prof. Dr. O. Ito
Institute of Multidisciplinary Research for Advanced Materials
Tohoku University, Katahira, Sendai, 980-8577 (Japan)

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Molecular imaging of pure C_{60} and its derivatives by STM has been reported.^[8–15] In general, the STM observations of fullerenes were conducted in an ultrahigh-vacuum (UHV) environment by using epitaxial adlayers prepared by sublimation. The sublimation technique, however, can not be applied to the preparation of C_{180} films, because of the ready thermal decomposition of C_{180} to C_{60} , as observed in the mass spectral analysis (APCI). Recently, we found a simple preparation for, and in situ STM observation of, fullerene epitaxial adlayers, based on a “wet process” in which the measurements were conducted under ambient conditions.^[14, 15] The simple transfer of Langmuir films at the air–water interface allowed us to prepare epitaxial adlayers of fullerenes on Au(111) surfaces. The formed epitaxial adlayers of C_{60} and C_{60}/C_{70} were found to be essentially the same as those prepared by sublimation in UHV.^[14, 15] Therefore, we attempted the application of this technique to the preparation of the C_{180} adlayers for STM imaging.

The Langmuir films of each of the fractions A, A2, and B of the C_{180} isomers at the air–water interface were transferred onto an intact Au(111) surface in a single step by passing the Au(111) surface through the air–water interface.^[14] As in the case of dimer C_{120} , π -A isotherms of C_{180} revealed only small surface pressures of less than several nm^2m^{-1} . Because of the lack of amphiphilicity, it seemed impossible to form an ideal monolayer of C_{180} . In this technique, the Langmuir films were used only to introduce materials at the monolayer level. After the transfer, the sample was placed in an electrochemical STM cell filled with 0.1M perchloric acid. The details of sample preparation and the in situ STM observation technique have been described.^[14, 15] The combination of the wet-process preparation using transfer of Langmuir films to Au(111) with in situ STM observation is advantageous, since a more uniform sample surface is obtained than that given by the casting of C_{180} from the organic solution and STM observation under air.

The surface morphologies of C_{180} adlayers were completely different from those of C_{60} . Figure 2 shows typical STM images of the C_{180} adlayers (fraction A2 and fraction B) and C_{60} adlayer on Au(111) surfaces. As mentioned above, the image of C_{60} revealed ordered molecular adlayers with hexagonal packing, although the films had many disordered regions (Figure 2C). In contrast, the C_{180} fractions (Figure 2A and B) gave entirely disordered adlayers and no ordered region was observed. The disordered adlayers are probably caused by a stronger interac-

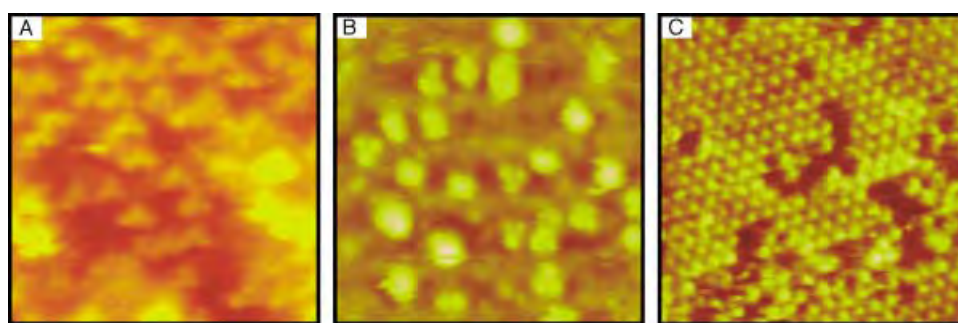


Figure 2. Typical in situ STM images for fraction A2 (A; $16.5 \times 16.5 \text{ nm}^2$) and fraction B (B; $12.2 \times 12.2 \text{ nm}^2$) of randomly adsorbed C_{180} adlayers and of a C_{60} epitaxial adlayer (C; $18.2 \times 18.2 \text{ nm}^2$) on Au(111) surfaces. Images A and B were collected with $E_s = 0.36$ and 0.38 V , $E_{\text{tip}} = -0.40$ and -0.41 V versus saturated calomel electrode (SCE), and $I_t = 0.38$ and 0.9 nA , respectively. Image C was collected with $E_s = 0.10 \text{ V}$, $E_{\text{tip}} = -0.05 \text{ V}$, and $I_t = 1.0 \text{ nA}$. There is no significant influence of sample potentials upon the observed images.

tion between C_{180} and the substrate (Au(111)). Submolecular high-resolution STM images are expected to reveal the structural differences among the C_{180} isomers. The disordered adlayer may facilitate the recognition of the isolated C_{180} isomers, which appear as several distinct structures lying flat on the surface. These structures consist of three bright spots, which correspond to each of the C_{60} moieties of C_{180} . The shape of C_{180} in fraction B appears quite different from that in fraction A2 (Figure 2).

Fraction B (Figure 2B) was expected to contain an isomer with significantly different structural characteristics from other isomers, because it gave a single peak under the two different HPLC conditions (Figure 1). Bright spots arranged in a triangular shape can be clearly recognized in Figure 2B.

Figure 3 shows typical high-resolution STM images of the C_{180} isomer in fraction B. It was found to have a cyclic triangular shape. The triangular shape with high symmetry is clearly attributable to the flat-lying “*cis-2/cis-2/cis-2*” isomer. The observed distance between spots in the cyclic feature is $0.7\text{--}0.8 \text{ nm}$, which is obviously smaller than the intermolecular distance, 1.0 nm , observed in the C_{60} epitaxial lattice. Thus the possibility of an accidental triangular assembly of three C_{60} molecules on Au(111) lattices is clearly ruled out. No other image, which could be attributed to other isomers, was observed in fraction B.

Ab initio molecular orbital calculations of the total electron energy (ΔE_{tot}) using HF/3-21G afford information about the

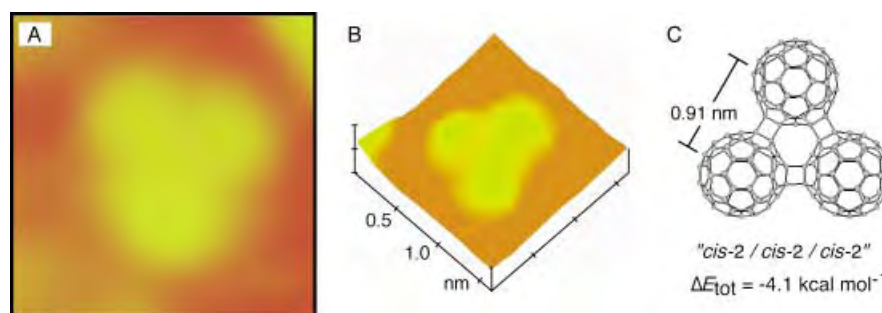


Figure 3. Typical high-resolution STM images of a C_{180} molecule on Au(111) surfaces prepared from fraction B, A) top view, $1.67 \times 1.67 \text{ nm}^2$, B) surface plot, and C) the chemical structure of the cyclic “*cis-2/cis-2/cis-2*” isomer. The image was collected with $E_s = 0.38 \text{ V}$, $E_{\text{tip}} = -0.41 \text{ V}$, and $I_t = 0.9 \text{ nA}$.

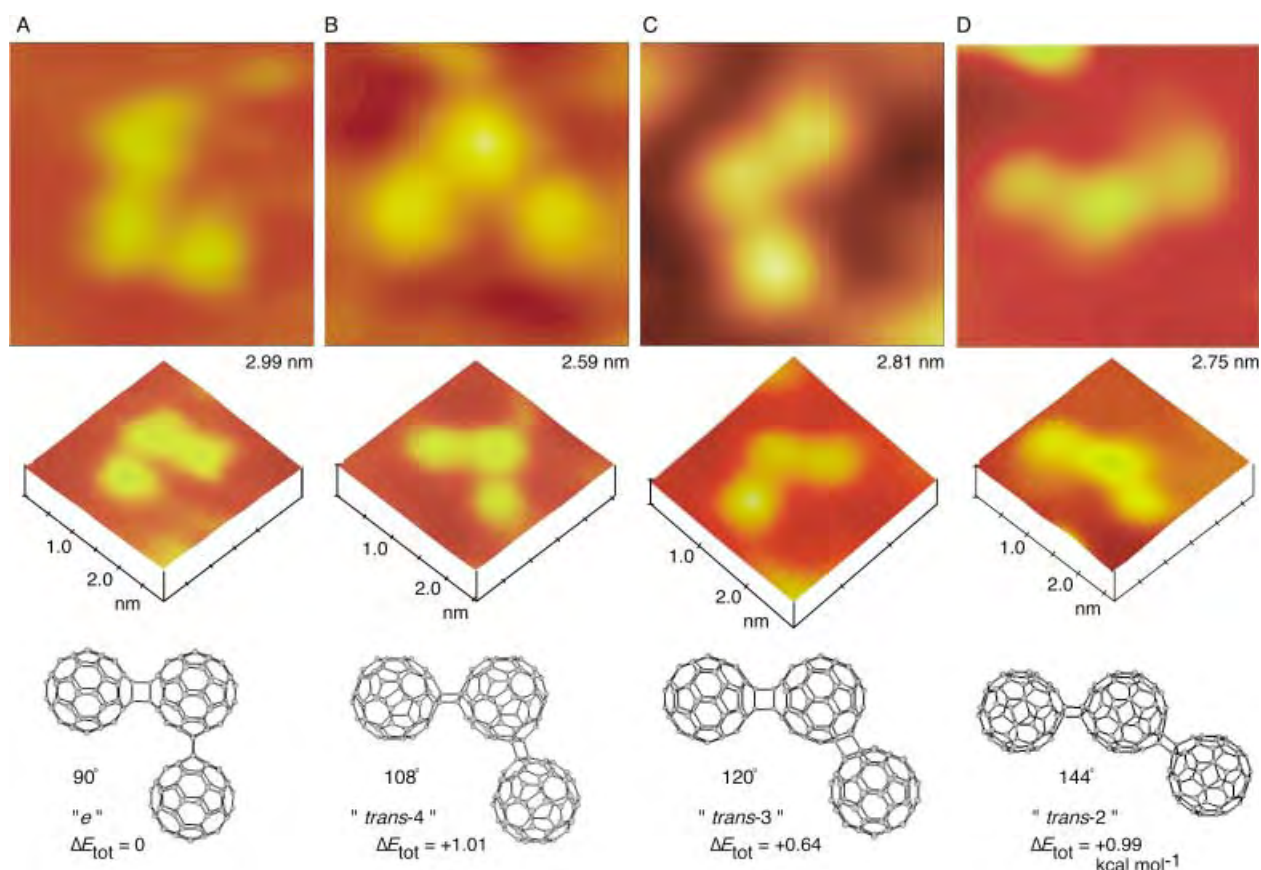


Figure 4. A variety of high-resolution STM images (top view and surface plot, below) of C_{180} molecules obtained from fraction A, and the chemical structures of the corresponding isomers. The images were collected with $E_s = 0.36$ V and $E_{tip} = -0.28$ V.

relative stabilities of the C_{180} isomers. Of the expected isomers, which include noncyclic isomers, the “*cis-2/cis-2/cis-2*” isomer was found to be the most stable (-4.1 kcal mol $^{-1}$ relative to the “*e*” isomer; Figure 4). STM images obtained from fraction A exhibited mixed structures consisting of four isomers, which possessed “noncyclic extended” structures (Figure 4). Each C_{180} molecule in the STM images appears as three spots connected at specific angles. The observed fold angles were approximately 90, 108, 120, and 144°, which can be attributed to “*e*”, “*trans-4*”, “*trans-3*”, and “*trans-2*” isomers, respectively. Neither the cyclic “*cis-2/cis-2/cis-2*” isomer nor the noncyclic “*cis*” isomers with a fold angle of less than 90° were observed.

The ratio of isomer content in fraction A was roughly estimated by counting the observed shapes of more than 100 molecular features in STM images. This surface content ratio should approximately reflect the content of each isomer in the whole of fraction A. The content ratios for “*e*”, “*trans-4*”, “*trans-3*”, and “*trans-2*” isomers were found to be 58, 25, 13, and 4%, respectively.

In addition, the STM image of fraction A2, which gave the largest analytical HPLC peak among the peaks in fraction A and was successfully isolated, indicated that this fraction is composed of only the “*e*” isomer of C_{180} . This result is in agreement not only with the isomer content in fraction A but also with molecular orbital calculations which predict the highest stability for this isomer of all the isomers with extended structures. The ΔE_{tot} values calculated by HF/3-

21G for “*trans-4*”, “*trans-3*”, “*trans-2*”, and “*trans-1*” isomers were +1.01, +0.64, +0.99, and +0.90 kcal mol $^{-1}$ relative to the “*e*” isomer, respectively. On the other hand, the small difference in the calculated ΔE_{tot} values among the isomers is reflected in the observation of STM images, which indicated that several isomers are simultaneously produced by the HSVM treatment of C_{60} . Interestingly, the “*trans-1*” isomer was hardly observed in fraction A. Statistically, the possibility that C_{60} will react at the “*trans-1*” position of C_{120} is 1/4 of the possibility of reaction at other positions of C_{120} , which gives the “folded” isomers. This low probability may be one of the reasons for the absence of the “*trans-1*” isomer.

In conclusion, we succeeded in the direct observation of thermally and photochemically labile C_{180} isomers by the transfer of Langmuir films onto Au(111) surfaces. The components of HPLC A and B peaks were clearly identified. The content ratio of the isomers was also determined by STM observation, which was in good agreement with the ΔE_{tot} values obtained by molecular orbital calculations. Thus, STM has, for the first time, been successfully applied to identify the isomeric structures of C_{60} trimers, which are difficult to determine spectroscopically, as a result of their extremely low solubility.

Examination of the unique electronic and spectroscopic characteristics of these C_{180} isomers^[17] is in progress to put them to use in electronic and photonic devices.

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Computational Prediction of the Phase Transformation of Two As-Synthesized Oxyfluorinated Compounds into the Zeotype CHA Forms

Stéphanie Girard, Alain Tuel, Caroline Mellot-Draznieks, and Gérard Férey*

The numerous syntheses of templated inorganic open frameworks in hydrothermal conditions^[1] were the starting point for the development of porous solids obtained by calcination, with applications as molecular sieves, for adsorption or catalytic purposes. Indeed the structure-directing agents, used during the synthesis of such compounds, are often incorporated in the final structure. Upon thermal treatment

(calcination), these template molecules can usually be removed, along with other species, such as water molecules and hydroxy groups. However, whereas the crystal structures of as-synthesized solids are well characterized, those of calcined solids, which are of crucial interest, are scarcely described, this is because of their powder form and a result of the difficulties of ab initio resolution from powder data.

Fortunately, in the last ten years, computational tools have proved their efficiency for simulating the structures and energetics of inorganic solids.^[2] Recently, we have successfully investigated the dehydroxylation process and organic-template extraction of two as-synthesized aluminophosphates, namely AlPO₄-14,^[3] and MIL-34.^[4] Starting from the knowledge of the as-synthesized structure only, all the atoms that are known to be eliminated upon calcination are removed. The so-modified AlPO₄-14 and MIL-34 model frameworks were then submitted to energy minimizations. This way, we predicted the calcined AlPO₄-14 structure in excellent agreement with the experimentally calcined AlPO₄-14,^[3] which had already been obtained before our calculations. Above all, we successfully anticipated the structures and energetics of the calcined form of MIL-34, before it was actually experimentally calcined. The cell parameters and atomic coordinates predicted from the simulation were used to perform the Rietveld refinement of the calcined sample powder pattern. The present work aims at developing a computational approach of the calcination process of fluorinated templated structures.

Indeed, fluoride ions can belong to the framework or act as template. In the continuously expanding number of synthetic oxyfluorinated AlPOs^[5,6] and GaPOs, which include three-dimensional (3D) frameworks with very large pores such as cloverite^[7] or MIL-31,^[8] fluoride ions may occupy one or two vertices of the Al/Ga polyhedra in terminal or bridging positions, such as in ULM-6^[5] or CJ2^[5] respectively, or act as anionic template, such as in cloverite,^[7] GaPO₄-LTA,^[9] and ULM-18,^[10] where they are encapsulated in D4R cages (Figure 1).

Regarding calcination, fluorine anions are deemed to play a specific role in the stabilization of the as-synthesized structure. This function is strongly related to their position in the framework and their high electronegativity, which often leads to strong hydrogen bonding and therefore a tighter amine–framework interaction. However, the mechanisms involved at the atomic scale during the calcination process are complex and still not clearly elucidated.

Here, we present the first attempt to use a computational approach to study the structural evolution during the dehydrofluorination process and template extraction of two isotopic as-synthesized oxyfluorinated open-framework structures, an aluminophosphate UT-6, (Al₆P₆O₂₄F)₂·(C₅H₅NH)₂·(H₂O)_{0.3},^[6] and a gallophosphate GaPO-tricl.CHA, (Ga₆P₆O₂₄F)₂·(C₄N₂H₆)₂·(H₂O).^[11] As shown from their X-ray diffraction (XRD) patterns, both structures adopt upon calcination the CHA zeotype,^[12] which correspond to the chabazite structure.

Herein, the experimental structures of the as-synthesized UT-6 and GaPO-tricl.CHA were taken as starting points for our simulations. UT-6 and GaPO-tricl.CHA are isostructural

[*] Prof. G. Férey, Dr. S. Girard, Dr. C. Mellot-Draznieks
 Institut Lavoisier, UMR CNRS 8637
 Université de Versailles Saint-Quentin
 45, Avenue des Etats-Unis, 78035 Versailles Cedex (France)
 Fax: (+33) 1-3925-4358
 E-mail: ferey@chimie.uvsq.fr
 Dr. A. Tuel
 Institut de Recherches sur la Catalyse, C.N.R.S.
 2 avenue Albert Einstein, 69626 Villeurbanne Cedex (France)

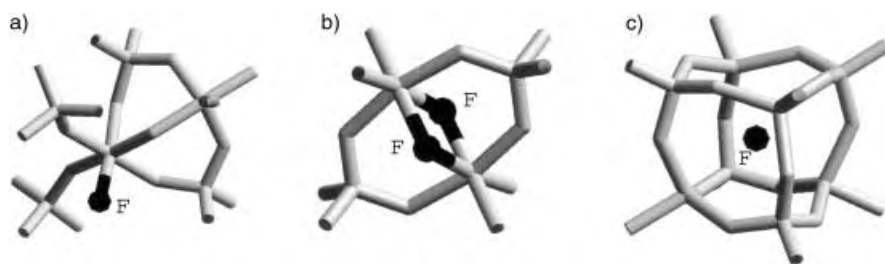


Figure 1. Various environments for the fluorine atoms in microporous inorganic structures. Typical fragments are extracted from existing crystal structures, F atoms in black. a) Terminal position (CJ2, MIL-14, ULM-13), b) bridging position (UT-6, GaPO₄-tricl.CHA), c) encapsulated position (cloverite, GaPO₄-LTA).

3D structures containing cages and three independent eight-membered-ring channel systems, with two template molecules trapped in each cage (Figure 2). The framework topology for each of the two as-synthesized compounds is closely related to that of neutral AlPO₄-CHA, which is constructed from D6R cages connected by four-ring windows. In the case of the fluorinated structures, each six-ring of the D6R cages contains one octahedral aluminum or gallium atom that connects to that of another hexagonal prism through two Al-F-Al or two Ga-F-Ga bridges, respectively (Figure 3a). Among the three inequivalent aluminum or gallium atoms present in the asymmetric unit, only one belongs to such an AlO₄F₂ or GaO₄F₂ octahedron, while the two others belong to AlO₄ or GaO₄ tetrahedra, as indicated on Figure 3a.

Prior to energy minimizations, all the atoms which are thought to leave the structures upon calcination were removed in both structures, that is, the bridging fluorine anions, the water molecules, and the pyridinium template cations (UT-6) and the 1-methylimidazole cations (GaPO₄-tricl.CHA). This approach results in “virtually” calcined neutral structures, with Al(Ga)PO₄ compositions, where all Al (Ga) and P atoms are tetracoordinate. However, these artificially modified structures retain the Al2 or Ga1 atoms from the original structures in highly distorted environments that emanate from the elimination of the bridging fluorine anions in both structures (Figure 3b). In a final step, both modified structures were submitted to constant pressure energy minimizations in the original space group *P* $\bar{1}$.

The calculations were carried out using the GULP code.^[13] The interatomic potentials used for UT-6 were those developed by Gale and Henson for aluminophosphates^[14] and, for GaPO₄-tricl.CHA, those developed by us

for simulating microporous gallophosphates.^[15] These force fields have been shown to reproduce experimentally determined structures of a series of aluminophosphates,^[15] respectively, with a good accuracy.

The key result of energy minimizations is that the initial models of calcined UT-6 and GaPO₄-tricl.CHA rapidly converge towards the CHA zeotype, that is, Al(Ga)PO₄-CHA, with all the metal atoms in regular tetrahedral environments (Figure 3c). Fig-

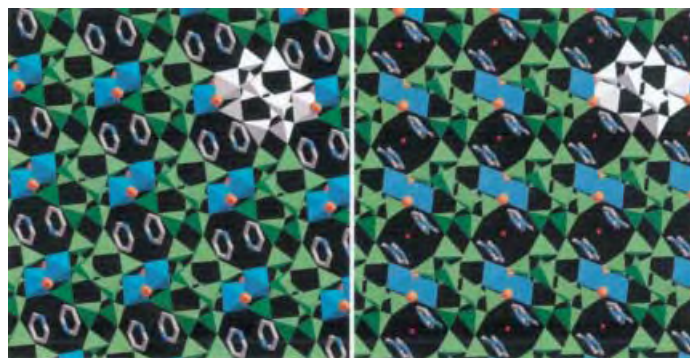


Figure 2. Polyhedral representation of the as-synthesized UT-6 (left) and GaPO₄-tricl.CHA (right) structures along the [010] and [100] directions, respectively. All AlO₄, GaO₄, and PO₄ tetrahedra are represented in green, while AlO₄F₂ and GaO₄F₂ polyhedra are shown in blue. F atoms: orange spheres, water molecules: red, and template molecules: gray cylinders. A hexagonal prism (D6R cage) is highlighted in white on each structure.

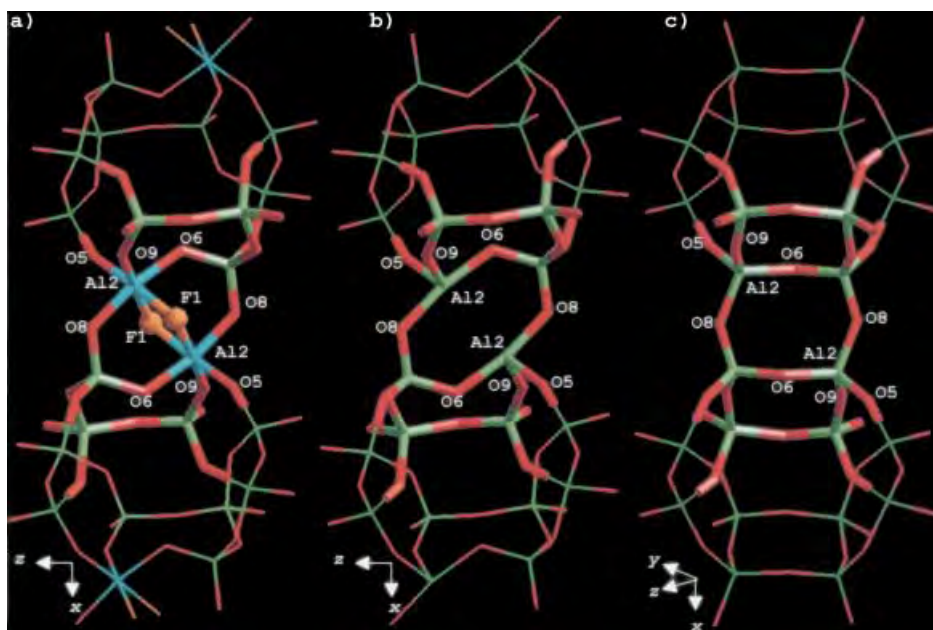


Figure 3. Framework fragment extracted from UT-6 which represents, up and down, two different D6R cages linked by two Al2 octahedra (hexacoordinate metal atoms are shown in blue, tetracoordinate in green, oxygen atoms in red, fluorine atoms in orange). a) In the as-synthesized structure, Al2 atoms are hexacoordinate at the center of AlO₄F₂ octahedra. b) After the removal of F atoms and prior to the calculations, Al2 atoms are in highly distorted tetrahedral environment. c) After energy minimizations, the predicted calcined UT-6 shows all Al atoms in regular tetrahedral environments. Selected bond lengths [Å] and angles [°] are also given for both the as-synthesized: Al2-O5 1.824, Al2-O6 1.874, Al2-O8 1.900, Al2-O9 1.824; O8-Al2-O9 90.8, O8-Al2-O6 169.9; predicted calcined structures Al2-O5 1.726, Al2-O6 1.721, Al2-O8 1.734, Al2-O9 1.716; O8-Al2-O9 107.2, O8-Al2-O6 112.5.

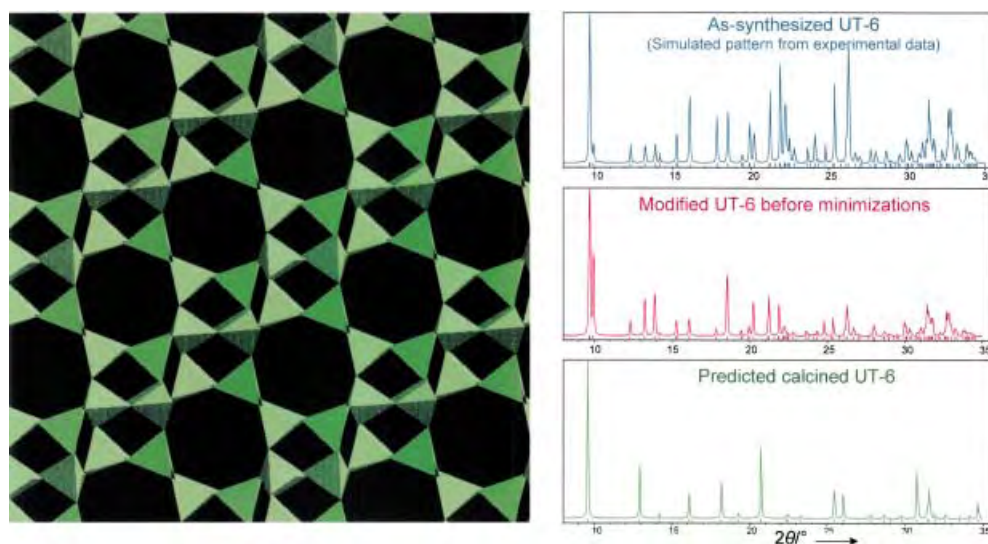


Figure 4. Calcined UT-6 as predicted by our energy minimizations in tetrahedral representation along with its simulated X-ray powder pattern (in green), the pattern of the as-synthesized structure after the removal of template molecules, water molecules, and F atoms and before minimizations (in red) and the pattern of the full original as-synthesized UT-6 (in blue).

Figure 4 shows the whole predicted calcined $\text{AlPO}_4\text{-CHA}$ zeotype structure. A careful examination of the minimized structures shows that both compounds undergo a change of symmetry from $P\bar{1}$ in their as-synthesized forms, into $R\bar{3}$ in their calcined forms. Table 1 gathers the simulated and experimental data when available, with a comparison of the atomic coordinates between the predicted and experimental

Table 1. Comparison between the simulated and experimental data (for the aluminophosphate only) for the predicted calcined forms of $\text{AlPO}_4\text{-CHA}$ and $\text{GaPO}_4\text{-CHA}$.^[a]

Space group	$\text{AlPO}_4\text{-CHA}$			Method
	a [Å]	b [Å]	c [Å]	
$R\bar{3}$	13.8381(1)	13.8381(1)	14.9365(1)	exp
$R\bar{3}$	13.6932	13.6932	14.6411	calcd
atoms	x/a	y/b	z/c	
P	0.89155	0.56139	0.44112	exp
	0.89777	0.55726	0.43533	calcd
Al	0.66282	0.55810	0.43589	exp
	0.67451	0.56410	0.44544	calcd
O1	0.59272	0.67019	0.65639	exp
	0.58619	0.65853	0.67858	calcd
O2	0.64871	0.01042	0.50019	exp
	0.64564	0.98722	0.49595	calcd
O3	0.79166	0.57395	0.46494	exp
	0.78435	0.57024	0.47006	calcd
O4	0.91205	0.80410	0.12282	exp
	0.88928	0.80054	0.12860	calcd
$\text{GaPO}_4\text{-CHA}$				
space group	a [Å]	b [Å]	c [Å]	
$R\bar{3}$	unknown	unknown	unknown	exp
$R\bar{3}$	13.845	13.845	13.849	calcd

[a] Experimental calcined $\text{AlPO}_4\text{-CHA}$ was obtained upon calcination of its triclinic templated form, and the latter was synthesized in the fluoride medium using piperidine as templating molecule. The structure of experimental calcined $\text{AlPO}_4\text{-34}$ has been solved by Rietveld refinement of the X-ray powder diffraction pattern. This is described in details elsewhere.^[17]

calcined $\text{AlPO}_4\text{-CHA}$. Our results are in excellent agreement with the experimental findings.^[6, 11, 17, 18]

Our simulations not only successfully capture the experimental change of symmetry ($P\bar{1} \rightarrow R\bar{3}$) upon calcination, but also give its atomic-scale interpretation. Indeed, such higher symmetry emanates mainly from the regularization of the four-rings, $\text{T}_2\text{P}_2\text{O}_{12}$ ($\text{T} = \text{Al}$ or Ga), because of both local and cooperative readjustment of the framework upon lattice energy minimizations (Figure 3b,c).

Figure 4 shows the simulated pattern of calcined $\text{AlPO}_4\text{-CHA}$. It is in excellent agreement with the experimental^[6, 17] one. For completeness, the simulated pattern of the experimental as-synthesized UT-6 compound is given, as well as the simulated pattern of the same structure after removal of F atoms and extra-frameworks species prior to energy minimizations, further illustrating the phase transformation occurring upon calcination. A similar agreement was obtained in the case of $\text{GaPO}_4\text{-CHA}$.^[11]

Then, the lattice energies per tetrahedral site (T site) of our initial ($-12455.75 \text{ kJ mol}^{-1}$ for UT-6 and $-12402.83 \text{ kJ mol}^{-1}$ for $\text{GaPO}_4\text{-tricl.CHA}$) and final models are compared with the energies of the related dense structures, that is, α -berlinite ($-12936.40 \text{ kJ mol}^{-1}$) and $\text{GaPO}_4\text{-quartz}$ ($-12925.56 \text{ kJ mol}^{-1}$). The calcined UT-6 ($-12927.84 \text{ kJ mol}^{-1}$) is 8.56 kJ mol^{-1} per T site less stable than α -berlinite, while the calcined $\text{GaPO}_4\text{-tricl.CHA}$ ($-12913.72 \text{ kJ mol}^{-1}$) is $11.84 \text{ kJ mol}^{-1}$ less stable than $\text{GaPO}_4\text{-quartz}$ per T site, which makes them relatively stable compounds. For comparison, the work of Henson et al. demonstrates that aluminophosphates are between 4 and 13 kJ mol^{-1} less stable than the thermodynamically favored dense polymorph, α -berlinite, under ambient conditions.^[16]

Herein, we have validated our computational “calcination” method on two isotopic structures containing fluorine atoms in their as-synthesized structures. This result shows that one may capture in one simple simulation step, the complex

successive processes involved during calcination of oxyfluorinated templated compounds, such as defluorination, dehydration, and template decomposition, and predict the related calcined microporous structure. In these cases, we show that there is no need to describe the whole thermodynamic cycle to gain valuable information concerning the phase transformation of an as-synthesized compound into its related neutral framework in terms of energetics and structures. Such a method may not be applied to the specific cases where the calcination involves complex atomic rearrangements such as topotactic transformations, but in many cases, simulation is able to anticipate the solid-state transformation of an anionic molecular sieve into its related neutral framework. This is also the first time that our method gives accurate prediction of the solid-state transformation on a gallophosphate structure.

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Assembly of a Face-to-Face Tetranuclear Copper(II) Complex as a Host for an Anthracene Guest**

Raymond Ziessel,* Loïc Charbonnière,
Michèle Cesario, Thierry Prangé, and
Hélène Nierengarten

The tailoring of sophisticated multitopic ligands that undergo metal-induced self-organization into well-defined architectures opens ways to the construction of organized supramolecular entities.^[1] Such systems may display, at the molecular level, useful recognition and catalytic properties^[2] and, at the macroscopic level, unusual mesomorphic^[3] and electronic behavior.^[4] Along these lines, it has been shown that rigid and linear polytopic ligands bearing bidentate chelating sites might self-assemble into well defined square-matrix arrays of metal centers without apparent defects following the general principle of maximum coordination.^[5, 6] However, when flexible ligands are used the previous ideal situation is not effective anymore, instead, host–guest complexes have been characterized, in which an uncomplexed ligand is embedded into the structure.^[7] The inclusion of a guest in a metal-containing architecture is an attractive property because it provides unique opportunities to study bimolecular reactions in microenvironments.^[2, 8]

As a first step toward the catalytic transformation of guest molecules encapsulated in a macrocyclic groove containing photo- or electroactive metals, we report that the use of a ditopic phenanthroline (phen) ligand bearing a spiro[5.5]undecane spacer provides, upon complexation with copper(II) cations, a face-to-face arrangement together with an intertwined texture as minor species.

Here the self-inclusion of a free ligand is not observed but motion around the methylene linkage provides two types of supramolecular organization based on a linear or orthogonal arrangement of the phenanthroline subunits. Furthermore, the capability of the complex to exhibit an ideal cleft for flat polycyclic hydrocarbons prompted us to study the inclusion of

[*] Dr. R. Ziessel, L. Charbonnière
Laboratoire de Chimie Moléculaire, ECPM
25 rue Becquerel, 67087 Strasbourg Cedex 02 (France)
Fax: (+33) 3 90 24 26 89
E-mail: ziessel@chimie.u-strasbg.fr

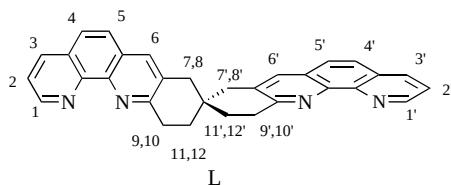
M. Cesario
Institut de Chimie des Substances naturelles, CNRS
91128 Gif-sur-Yvette (France)
T. Prangé
LURE Bât. 209d, Université Paris-Sud
91405 Orsay (France)

H. Nierengarten
Laboratoire de Spectrométrie de Masse Bio-organique, ECPM
25 rue Becquerel, 67087 Strasbourg Cedex 02 (France)

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anthracene, naphthalene, and pyrene within the macrocyclic structure.

The spiro-bridged bisphen ligand **L** (Scheme 1) was prepared by a Friedländer condensation between 8-amino-7-quinolinecarbaldehyde and 3,9-diketospiro[5.5]undecane as reported.^[9] When ligand **L** was allowed to react with



Scheme 1. Numbering scheme of **L**.

one equivalent of $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{X}$ ($\text{X} = \text{BF}_4, \text{ClO}_4, \text{PF}_6$) a deep-orange solution was instantaneously formed from which an orange–red solid precipitated upon the addition of diethyl ether. Elemental analysis data is consistent with $\{\text{Cu}(\text{L})(\text{X})\}_n$ and the deep-orange color (UV/Vis: $\lambda_{\text{max}} = 449 \text{ nm}$, $\epsilon = 3220 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$ per copper atom) arising from a metal-to-ligand charge transfer (MLCT) transition is characteristic of copper(I) surrounded in a tetrahedral fashion with four nitrogen atoms.^[10]

Electrospray mass spectrometry (ES-MS) was a convenient analytical tool^[11] to determine unambiguously the stoichiometry of this copper complex (Figure 1). Four peaks corresponding to the successive loss of BF_4^- ions are observed (m/z 516.3 for $[\text{Cu}_4\text{L}_4]^{4+}$, 717.2 for $[\text{Cu}_4\text{L}_4(\text{BF}_4)]^{3+}$, 1119.2 for $[\text{Cu}_4\text{L}_4(\text{BF}_4)_2]^{2+}$, and 2325.0 for $[\text{Cu}_4\text{L}_4(\text{BF}_4)_3]^+$). Furthermore, the isotopic pattern obtained for the most intense pseudo-molecular ion at m/z 516.3 confirms the 4+ charge state of a tetranuclear complex. Interestingly, similar results are obtained using the PF_6^- and ClO_4^- salts.

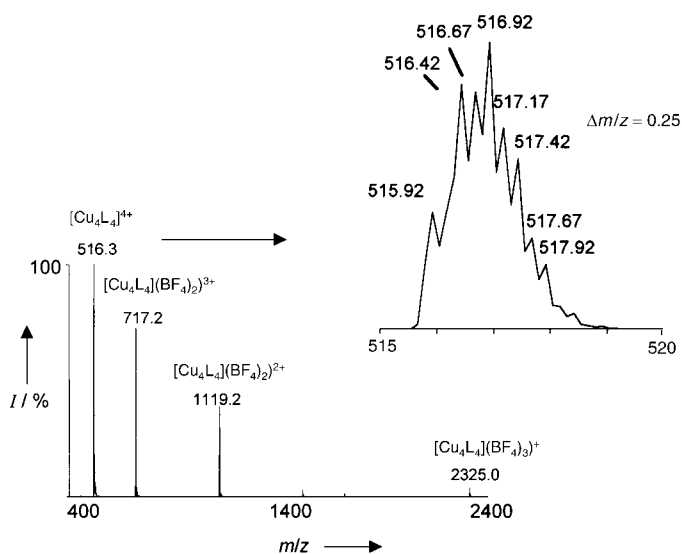


Figure 1. ES mass spectrum of an equimolar mixture of **L** and $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4$ in CH_3CN (10^{-4} M) and isotopic pattern obtained for the peak at m/z 516.3. Isotopic peaks are separated by 0.25 m/z units confirming the charge state (4+) of the ion depicted in the insert.

From these data it becomes obvious that a cyclic tetranuclear complex of generic formula $[\text{Cu}_4\text{L}_4](\text{BF}_4)_4$ was obtained. The different ways to intertwine the ligand around four tetrahedral metal centers are represented in Figure 2. While rigid bidentate ligands bearing parallel binding sites uniformly gave face-to-face structures of type **1**,^[5,6] the introduction of flexibility between these sites or antiparallel binding vectors introduces new structures such as the plaited form **2**,^[12] and the hybrid architectures **3** and **4**.^[13]

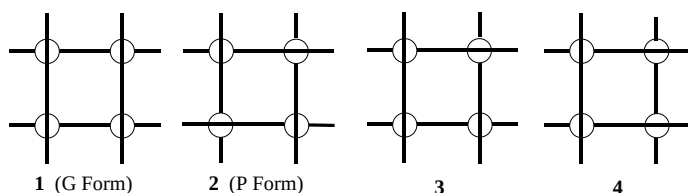


Figure 2. Possible ways of linking four tetrahedral metal centers (○) with four ligands **L**.

In CD_3CN , the ^1H NMR spectrum of the isolated amorphous $[\text{Cu}_4\text{L}_4](\text{BF}_4)_4$ material displays two families of protons (Figure 3b). The first family, which corresponds to the major

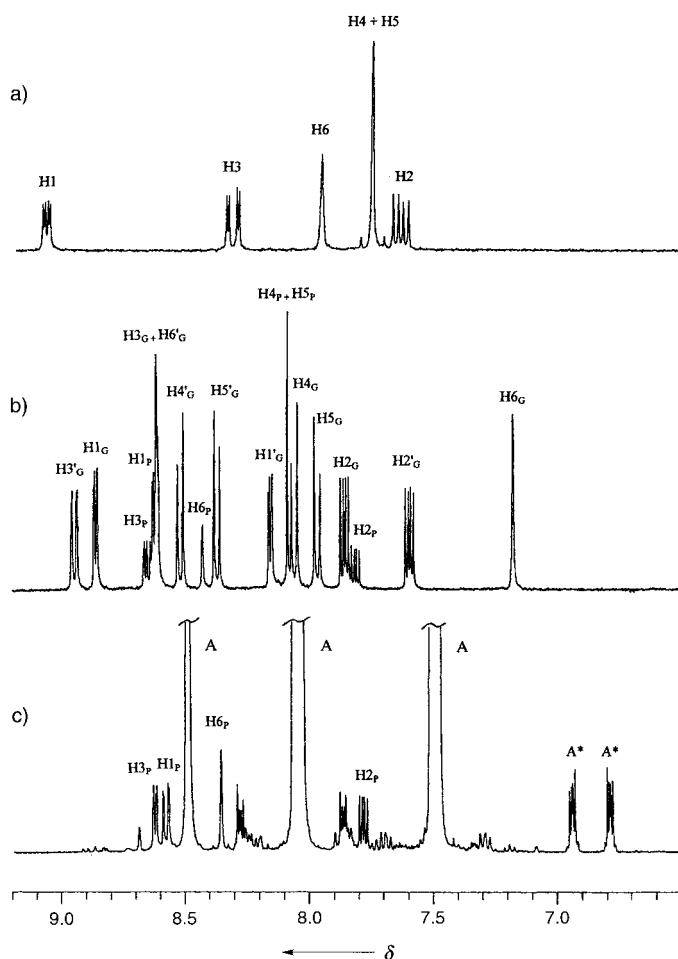


Figure 3. ^1H NMR spectra of the aromatic part of a CD_3CN solution of: a) ligand **L**; b) $[\text{Cu}_4\text{L}_4](\text{BF}_4)_4$; c) $[\text{Cu}_4\text{L}_4](\text{BF}_4)_4$ in the presence of 30 equivalents of anthracene. Proton numbering corresponds to the numbering in Scheme 1 with G and P for the face-to-face and plaited structures, respectively, A = free anthracene, A* = intercalated anthracene.

species, comprised 12 signals from aromatic and 12 from aliphatic protons all integrating for one proton, while the second set displayed 10 resonance signals with the same integral values and a peak of twice this value. Simple symmetry considerations rapidly eliminate possibilities **3** and **4** (Figure 2) as a result of the inherent lack of symmetry elements. The presence of a spirobicyclic spacer between the two phen subunits precludes the possibility of vertical planes of symmetry in structure **1** giving an overall D_2 symmetry group which leads to 12 resonance signals for the aromatic protons. With all six methylene groups being stereotopic, 12 resonance signals from aliphatic hydrogen atoms are expected and are indeed observed. For the minor species, a plaited structure **2** is suggested, because of the presence of a set of two C_2 axes perpendicular to the main axis and passing through the spiro carbon atoms, thus leading to a D_4 symmetry group. Consequently, the number of nonequivalent aromatic protons is reduced to six. Full assignment of the protons of the ligand in each family was achieved by two-dimensional (2D) COSY and NOESY experiments (Table 1).

Table 1. Chemical shift values for the protons of the ligand in the face-to-face structure **1**, the plaited structure **2** and the free ligand L.^[a]

Proton	Form 1	Form 2	Free ligand L
H1	8.87	8.16 ^[b]	8.64
H2	7.86	7.60 ^[b]	7.68
H3	8.62	8.95 ^[b]	8.35
H4	8.06	8.52 ^[b]	7.80
H5	7.97	8.38 ^[b]	7.80
H6	7.18	8.61 ^[b]	8.00
H7, H8	0.62, 2.67	2.17, 2.75 ^[b]	3.08, 3.23
H9, H10	1.70, 1.24	−0.31, 2.70 ^[b]	2.97, 1.53
H11, H12	1.35, 2.21	0.74, 2.37 ^[b]	1.71, 2.20

[a] The numbering scheme is provided in Scheme 1. [b] Refers to the part of the molecules numbered with a prime.

In the face-to-face structure **1**, the two phen subunits of a single ligand can be distinguished. Some drastic upfield shifts can be observed with respect to the free ligand (see H6_G, H7_G, H9_G, and H11_G in Table 1 and Figure 3); it is surmised that those protons are located in the shielding region of a neighboring spiro-phen molecule. Nuclear Overhauser enhancement (NOE) correlations between H6_G and H4'_G, H6_G and H3'_G, and H5_G and H3'_G revealed dipolar interactions between the phen subunits corresponding to interactions with two ligands in a parallel configuration of type **1**. Assuming that the thermodynamic equilibrium was reached during the assembly process leading to the tetranuclear complexes, the ratio of both structures allows for calculation of the energy difference and shows the face-to-face structure to be 3.8 kJ mol^{−1} more stable than the plaited structure. Furthermore, field-dependent measurements and saturation-transfer experiments did not reveal any chemical exchange between these structures and a lower limit of 73.3 kJ mol^{−1} can be calculated for the activation energy necessary for chemical exchange between the two forms.

The crystal structure of the major complex unambiguously confirms a tetranuclear macrocyclic arrangement and the asymmetric unit consists of discrete [Cu₄L₄]⁴⁺ and PF₆[−] ions (Figure 4a).^[14] The overall scaffold is a face-to-face structure

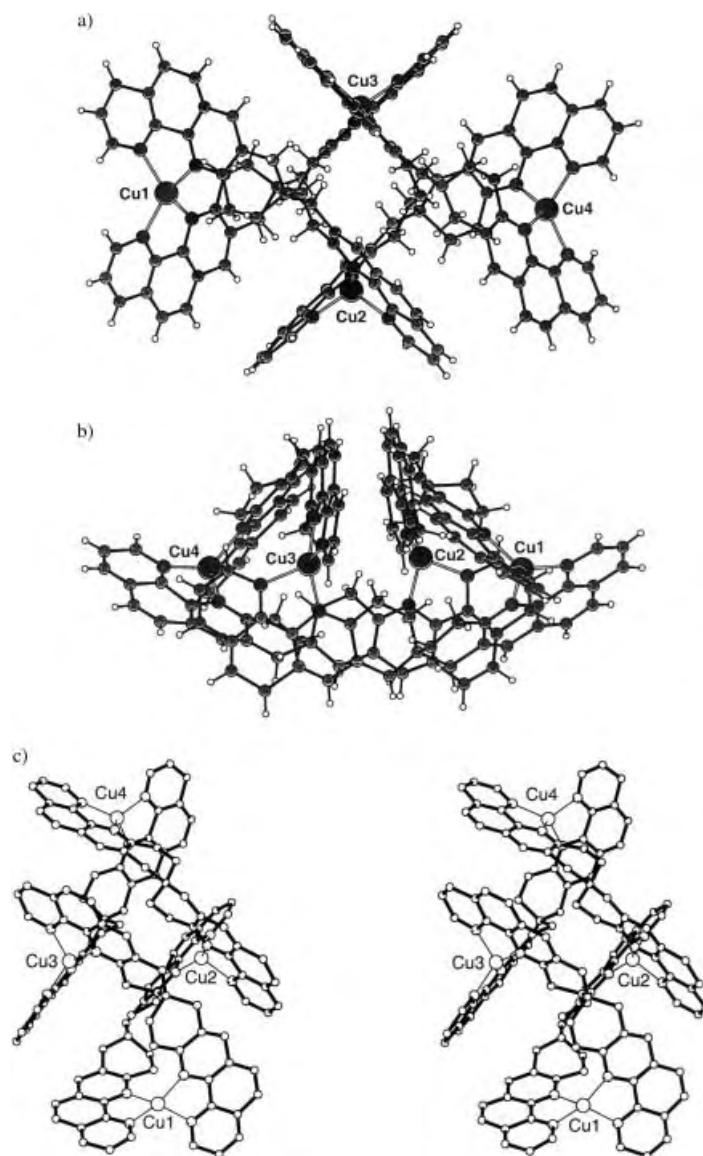


Figure 4. ORTEP representations of the tetranuclear [Cu₄L₄]⁴⁺ complex: a) view along the pseudo- C_2 axis of the molecule; b) view orthogonal to the C_2 axis of the molecule; c) stereoview.

where the four copper atoms are tetrahedrally coordinated to two phen subunits belonging to two independent ligands. The four metal centers provide a quasi-planar arrangement with a root-mean-square deviation of 0.151(2) Å. Within this plane, the copper(II) ions are placed at the vertices of a rhombus of edge 8.5 Å, with an acute angle of 52°. Two kinds of distinct coordination for the copper atoms are found. For Cu1 and Cu4, placed at acute angles of the rhombus, the dihedral angles formed by the two coordinated phen mean planes (74.3 and 78.6°, respectively) reflect a flattening of the coordination tetrahedron, while for Cu2 and Cu3, the angles (91.5 and 88.6°, respectively) are very close to a conventional right angle. In a single ligand strand, the average dihedral angles defined by the phen mean planes vary around 49° (from 44–53°). The tetranuclear complex adopts a basket-shaped conformation (Figure 4b). The largest dimensions of the basket are 21.6 Å between the most extreme phen units and

9.0 Å in height. A striking result revealed by the crystal structure is the presence of a large pocket of about $7.4 \times 8.8 \text{ Å}^2$, auspicious for the intercalation of planar substrates. A stereoview of the molecular structure is provided in Figure 4c.

A very interesting feature was observed by ^1H NMR spectroscopy, upon addition of excess anthracene the signals corresponding to the face-to-face structure drastically decrease and a plethora of new signals are seen, while signals corresponding to the plaited structure remain unchanged (Figure 3c). Furthermore, a new set of three signals can be observed at $\delta = 6.93$, 6.78 (Figure 3c), and 4.57 (not shown) integrating for two, two, and one protons, respectively. NOE differential experiments show these signals to be chemically exchangeable with those of anthracene, which suggests that they correspond to anthracene molecules in a particular chemical environment. Furthermore, assuming these new signals are from anthracene molecules, their integral values correspond, within experimental error, to the loss in intensity observed for the signals of the face-to-face structure. These results suggest that this latter structure can act as a host for one anthracene molecule (Figure 5b). This process, probably driven by π -stacking interactions with some phenanthroline subunits, causes large upfield shifts of the signals belonging to the intercalated guest and also leads to the disruption of the overall symmetry of the superstructure. This loss of symmetry results in a splitting of the original signals of the face-to-face compound into numerous new peaks ($\delta = 7.17\text{--}7.38$, $7.66\text{--}7.73$, $7.82\text{--}7.91$, $8.17\text{--}8.30$, Figure 3c) some of them being hidden by the intense anthracene signals. In contrast, the plaited structure does not allow inclusion of anthracene and its signals remain unperturbed. An estimated value of $(5.8 \pm 0.9) \text{ M}^{-1}$ was calculated for the association of anthracene within the face-to-face structure.

To confirm the presence of electronic interaction between the macrocyclic host and the anthracene guest, cyclic voltammetric (CV) studies of solutions of the PF_6 complex were carried out. The tetranuclear complexes undergo a single but broad oxidative process at +0.56 V (full details of the CV experiment are in the Experimental Section) consistent with the oxidation of copper(I) to copper(II). The relatively high oxidative potential found for this complex is in keeping with those found for various copper(I)–phen compounds.^[15] The relatively large ΔE_p ($\Delta E_p = E_p^a - E_p^c$) for the oxidation wave (ca. 100 mV) indicates that it may result from multiple closely

spaced one-electron oxidations of each metal center. In addition, two ligand-based reductions at -1.48 V ($\Delta E_p = 65 \text{ mV}$) and -1.72 V ($\Delta E_p = 72 \text{ mV}$) are ascribed to the sequential reductions of each phen subunit surrounding the copper(I) centers. Each of these reduction peaks corresponds to four electrons compared to the four electrons released during the oxidation process. By adding 10–30 equivalents of anthracene no significant shifts of the copper-based oxidation and the first ligand-localized reduction could be observed, but the second ligand-based reduction shifted by 100 mV with a marked broadening of the redox wave. This observation is in keeping with the intercalation of anthracene which results in the increase of the electron density of the interacting phen fragments and consequently in a large cathodic shift. Attempts to determine the reduction potential of the encapsulated anthracene (above -1.95 V) were hampered by the use of a large excess of anthracene.

In conclusion, the results presented here provide a rational approach for the engineering of molecular scaffoldings. The introduction of moderate flexibility into the linkage between two phen subunits produced the inorganic face-to-face arrangement as the major species while tilting of the binding vectors provide a plaited arrangement (Figure 5a and 5c, respectively) Because of the size of the spiro ligand and the steric constraints imposed by the $[5 \cdot 5]$ linkage the π stacking of the phen units is not optimal, which leaves, in the face-to-face arrangement, open space for interaction with added cyclic aromatic guests, such as anthracene, naphthalene, or pyrene. The molecular recognition event has been investigated by cyclic voltammetry as well as by proton NMR spectroscopy which also show that in the plaited species the recognition of anthracene is not effective. This result is used to confirm the parallel configuration of the ligands in the major compound, a configuration confirmed by the solid-state X-ray structure. Copper(I)–phen complexes exhibit oxidative nucleic acid activity^[16] and because of the presence of similar centers in the present species, the capability to act as a microreactor for the catalytic oxygenation of the encapsulated anthracene guest is currently under investigation.

Experimental Section

ES-MS measurements were performed on a triple quadrupole mass spectrometer Quattro II (Micromass, Altrincham, UK). The ES source was heated to 80°C . The sampling cone voltage (V_c) was at 20 V to avoid any fragmentation processes. Sample solutions were introduced into the



Figure 5. Photographs of the Corey–Pauling–Koltun (CPK) molecular models of the tetranuclear complexes representing a) the face-to-face arrangement in perfect keeping with the X-ray structure; b) encapsulation of an anthracene substrate in the previous face-to-face arrangement; c) the plaited organization obtained by motion around the CH_2 linkage of the spiro linkers.

mass spectrometer source with a syringe pump (Harvard type 551111: Harvard Apparatus Inc., South Natick, MA, USA) with a flow rate of $4 \mu\text{L min}^{-1}$. Calibration was performed using protonated horse myoglobin. Scanning was performed in the MCA (multichannel analyzer) mode, and several scans were combined to obtain the final spectrum. Electrochemical studies were made by cyclic voltammetry with a conventional three-electrode system using a BAS CV-50 W voltammetric analyzer equipped with a Pt microdisk or a Hg Kemula hanging electrode as working electrode and a Ag wire counter electrode. Ferrocene ($E_{1/2} = +0.65 \text{ V}$) or paraquat ($E_{1/2} = -0.23$ and -0.60 V) were used as an internal standard with the Pt and Hg electrodes, respectively. Solutions contained the electrode-active substrate (ca. $5 \times 10^{-4} \text{ mol dm}^{-3}$) in deoxygenated and anhydrous DMF containing tetra-*N*-butylammonium tetrafluoroborate (0.2 mol dm^{-3}) as supporting electrolyte. The quoted half-wave potentials were reproducible within 15 mV .

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Frouin, *Rev. Sci. Instrum.* **1992**, *63*, 982–987) at the DCI synchrotron, LURE (Orsay-France) at $\lambda = 0.964 \text{ \AA}$, on a MAR-Research 345 image plate system. Image plate distance: 10 cm . A total of 100 frames, each 3° in rotation, were recorded and processed with the *hkl* package of the program (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326). As one of the twins was in greater percentage, it was possible to integrate only one component at the indexing level. $3.74 < \theta < 26.26^\circ$, $-24 \leq h \leq 24$, $0 \leq k \leq 15$, $0 \leq l \leq 27$. A total of 23225 reflections was obtained of which 5490 were independent and used to refine 809 parameters. 5462 observed reflections with $I > 2\sigma(I)$. $R = 0.0961$, $wR_2 = 0.2578$ (observed), $R = 0.0964$, $wR_2 = 0.2580$ (all data). The structure was solved by direct methods (SHELXS86) and refined on F^2 for all reflections by least-squares method (SHELXS93). Hydrogen atoms were introduced at their theoretical positions and refined with constraints on bond distances and angles. Isotropic thermal factors were kept at 1.2 times that of the bonded atom. Only copper, nitrogen, and phosphorus atoms were refined anisotropically to limit the number of parameters versus the number of data. Largest difference peak and hole are 0.82 and $-0.57 \text{ e \AA}^{-3}$, respectively. CCDC-170600 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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The Mechanism of Catalytic Enantioselective Fluorination: Computational and Experimental Studies

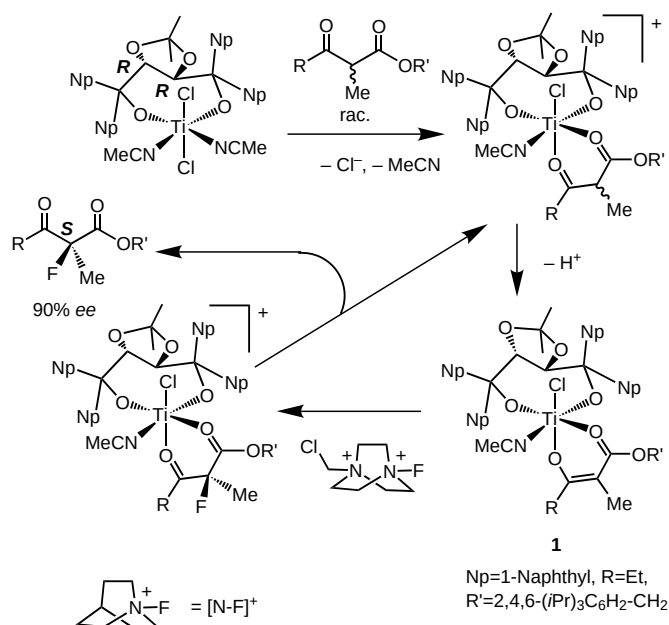
Stefano Piana, Ingrid Devillers, Antonio Togni,* and Ursula Rothlisberger*

Despite the undisputed importance of organofluorine compounds, for example, in biomedical applications, the generation of fluorinated carbon stereocenters by C–F bond-forming reactions remains rare and particularly challenging.^[1,2] Recently, the first catalytic, enantioselective fluorination of β -ketoesters with F-TEDA (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane; TEDA = triethylenediamine) in the presence of 5% of $[\text{TiCl}_2(\text{TADDOLato})]$ (TADDOL = α, α', α' -tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) catalysts was reported.^[3,4] We have shown that the reaction proceeds smoothly in acetonitrile at room temperature and the obtained enantioselectivity reaches 90% *ee* using a (*R,R*)-TADDOL bearing 1-naphthyl substituents.^[4] We assume, as a first mechanistic hypothesis, that

[*] Prof. Dr. A. Togni, Prof. Dr. U. Rothlisberger, Dr. S. Piana, Dr. I. Devillers
Laboratory of Inorganic Chemistry
Swiss Federal Institute of Technology, ETH Hönggerberg
8093 Zürich (Switzerland)
Fax: (+41) 1-632-1090
E-mail: togni@inorg.chem.ethz.ch, uro@inorg.chem.ethz.ch

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the β -ketoester coordinates to the catalyst as an enolate and substitutes one of the two chlorides and one of the acetonitrile molecules (Scheme 1). Thus, the octahedral monochloro Ti(enolato) complex **1** is the reactive species and is fluorinated by F-TEDA in the crucial C–F bond-forming step,^[4] the mechanistic details of which are still poorly appreciated.^[5–8]



Scheme 1. Simplified mechanistic hypothesis for the Ti-catalyzed asymmetric fluorination reaction. The $[\text{N-F}]^+$ ion reagent used in the computational studies is also shown.

To understand the origin of enantioselectivity and to elucidate the detailed mechanism of the actual fluorination step, we performed density functional theory (DFT) based mixed quantum mechanical/molecular mechanical (QM/MM) calculations on complex **1**. Using the program ADF2000^[9] in combination with a suitably modified version of the classical force-field AMBER95,^[9–11] we found that the eight possible stereoisomeric forms of complex **1** represent local minima on the energy hypersurface. In particular, the four most stable stereoisomers **1a–d** (Figure 1) have the chloride ligand in axial position, the equatorial plane being defined by the Ti center and the two coordinated TADDOL oxygen atoms. Each of the corresponding equatorial counterparts, obtained by exchanging the coordination positions of chloride and acetonitrile, are 4–6 kcal mol^{–1} less stable. The bonding parameters^[11] of the calculated structures **1a–d** are in excellent agreement with those reported recently for an analogous complex that contained a 1,3-diketono ligand and was characterized by X-ray crystallography.^[12] For the species **1a** and **1c** the enolate fragment and one of the two face-on oriented naphthyl groups are almost perfectly parallel (Figure 2). As a consequence, the *Re*-face of the enolate in **1a** (the *Si*-face in **1c**, respectively) is completely shielded and a fluorine atom can only be delivered from the opposite side. For the other two isomers **1b** and **1d** similar considerations apply to an edge-on oriented naphthyl group, but the effect

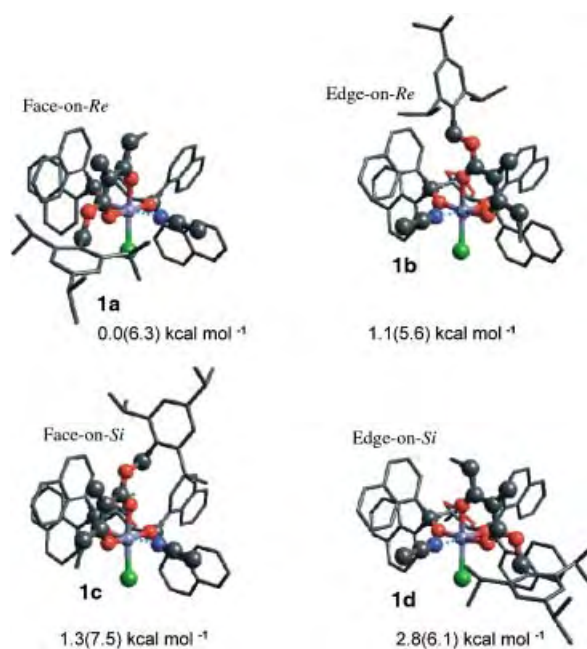


Figure 1. Structure and relative energies of the four most stable Ti(enolato) complexes with the chloro ligand (green) in axial position with respect to the plane of the Ti(TADDOLato) chelate. Hydrogen atoms are omitted for clarity. The energies of the corresponding stereoisomers with an equatorial chloride ligand are given in parenthesis. All the groups directly bound to the titanium were treated at the DFT level and are represented as balls and sticks. All other atoms are shown as sticks and were accounted for by a classical force field.^[10]

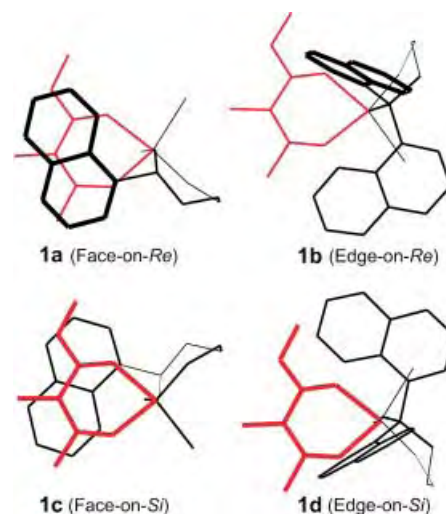


Figure 2. Schematic projections on enolate plane (red) for the calculated structures **1a–d** showing the shielding of one of the enolate enantiofaces by either a face-on or an edge-on naphthyl group (for a definition of face-on and edge-on orientations of aryl groups in TADDOLs, see ref. [3]).

appears to be less pronounced. The shielding situation in the most stable isomer **1a** correctly predicts the observed absolute configuration of the product.

There is a long-standing debate about the reaction mechanism for the electrophilic fluorination reaction with N–F reagents. In particular, it is controversial whether the reaction proceeds by a single-electron transfer (SET) or is a simple nucleophilic substitution ($\text{S}_{\text{N}}2$) at the fluorine atom.^[5–8] Two experimental observations have oriented our investigation. Firstly, a small amount (1–4%) of chlorinated by-product is

formed in the case of slow reacting substrates,^[13] with the source of chlorine being the catalyst. Secondly, the extent of chlorination can be enhanced up to 12–15 % by the addition of one equivalent of a chloride salt (NH₄Cl or NaCl). The enantioselective formation of the chlorinated product demonstrates the involvement of the catalyst in the side reaction. However, since F-TEDA is inert towards chloride,^[14] the origin of an electrophilic chlorinating agent under reaction conditions is not clear.

To further investigate these points we carried out QM/MM first-principles molecular dynamics^[15] studies of the fluorination step in vacuo and in acetonitrile solution.^[16] All the simulations were performed for a temperature of 300 K. The lowest energy complex **1a** was taken as a starting point and 1-fluoro-1-azonium-[2.2.2]bicyclooctane ([N–F]⁺ ion, which models F-TEDA, see Scheme 1) was added to the system.

The in vacuo simulations were started at a distance d_{C-F} of 3.5 Å between the C_α atom of the β-ketoester and the fluorine atom of the [N–F]⁺ ion. After a few femtoseconds, one electron is transferred from the Ti complex to the [N–F]⁺ ion. As a consequence, an antiferromagnetic diradical species is formed that is stable throughout the investigated time scale of a few picoseconds and no further spontaneous reaction is observed. This result is an indication that in vacuo the reaction proceeds by a SET involving the formation of a [N–F][•] radical, that however, does not automatically lead to product formation.

For the studies in acetonitrile solution, constrained molecular dynamics simulations were performed in which d_{C-F} was progressively reduced from 2.9 to 1.7 Å. This approach allowed the evolution of the system to be followed during the fluorination process and to eventually estimate the reaction free energy associated with this reaction step. In contrast to the in vacuo simulations, no spontaneous SET is observed even at d_{C-F} = 2.6 Å (Figure 3) as a result of the

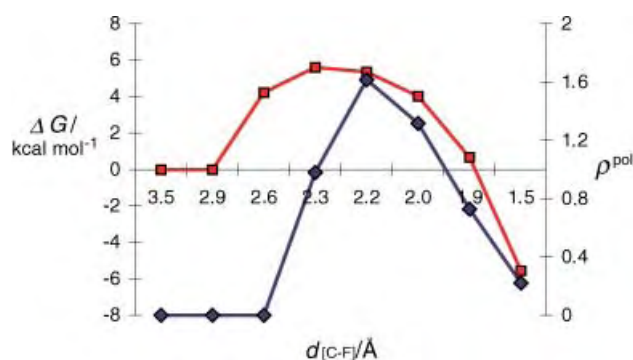


Figure 3. Approximate reaction free-energy profile for the catalytic electrophilic fluorination (red) as a function of the C–F distance [Å]. The integrated value of the absolute polarization spin density $\rho^{pol} = \int |\rho^{\alpha}(\vec{r}) - \rho^{\beta}(\vec{r})| dV$ is also indicated (blue). The total simulation time was 4.8 ps. After the simulation at d_{C-F} = 1.9 Å, the constraint was released and the system was simulated for another 0.3 ps.

additional stabilization of the [N–F]⁺ ion by the polar solvent. Upon further reduction of the constraint distance, the free energy increases and the average N–F distance elongates from 1.53(3) Å at d_{C-F} = 2.9 to 1.61(5) Å at d_{C-F} = 2.2 Å. At

the latter distance, one electron is transferred from the Ti complex to the [N–F]⁺ ion. Simultaneously, the N–F bond is broken and the force acting on the constraint changes its sign, thus indicating the crossing of the transition-state (Figure 3). Indeed, releasing the constraint at this point of the simulation leads to product formation within a few femtoseconds.

The relative stability of cationic versus radical form of the intermediate species depends crucially on the interaction with the solvent. It is therefore conceivable that because of the thermal fluctuations in the solvation shell, an alternative reaction pathway could become available. The dipole–charge interaction of the [N–F]⁺ ion with the solvent could eventually become small enough that, in analogy to the simulation in vacuo, a SET occurs before the transition state for the fluorine transfer is reached. In this case, an [N–F][•] radical would be formed. This radical could then react with the chloride present in solution leading to the formation of the relatively stable Cl[•] radical, which is ultimately responsible for the formation of the chlorinated by-product. In this case, a radical scavenger should be able to quench the chlorination, while not affecting the fluorination reaction.

In fact, we have found that the addition of 2,2',3,3',4,4',5,5'-octamethyl-1,1'-bis(*tert*-butylthio)ferrocene^[17] to the reaction mixture has a drastic effect. The extent of ethyl 2-methyl-3-oxo-3-phenylpropanoate chlorination is reduced to 10–20 % of the normal yield, while the fluorination is unaffected. Thus, by the addition of a one-electron donor it is possible to discriminate between the two halogenation processes. This result strongly supports the SET mechanism as a pathway for halogen transfer in these reactions.

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Supporting Information. Calculations performed on a larger system that included the whole TADDOL ring in the QM part give essentially the same results in terms of geometry and relative configurational energies.

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Molecular Dynamic Computer Simulations of Phase Behavior of Non-Ionic Surfactants

Ekaterina Ryjkina, Hubert Kuhn,* Heinz Rehage, Felix Müller, and Jörg Peggau

Surfactants, because of their varied operational possibilities, are one of the most important products for the pharmaceutical, plastic, and mineral oil industries. Research in this area plays a prominent role in interface and colloid science.

Depending on the temperature and concentration, surfactants are capable of building diverse, complex structures. The multifaceted behavior of amphiphilic substances in water in respect to aggregation activities is shown in Figure 1. At concentrations below the critical micelle concentration (cmc), surfactants tend to adsorb as a monolayer at the water–air interface. At concentrations above the cmc, they build spherical, rodlike, or disclike micelles. With further increases in the concentration of surfactant, they can occur as cubic as well as nematic, hexagonal, and lamellar mesophases.

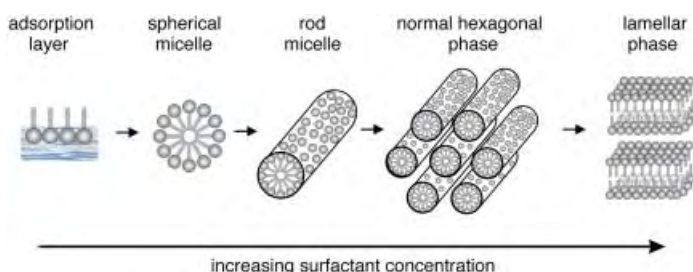


Figure 1. The building of structure and aggregation forms of surfactants in aqueous solutions depending on the surfactant concentration.

Such different aggregation forms exemplify the variety of surfactant characteristics.^[1] The determination of phases and complex structures for the prediction of washing and cleaning mechanisms of surfactants with experimental methods is very important; however, the measurements of phase diagrams and the characterization of complex structures are difficult, time-consuming, and costly.

Herein, we introduce a computer simulation method that allows an easier calculation and prediction of surfactant phases in the presence of water molecules. The results for the dodecyldimethylamine oxide (DDAO; Figure 2) aqueous system presented, show that the molecular dynamics in terms of dissipative particle dynamics (DPD) can lead to an improved understanding of the structure of surfactant aggregates in water, as demonstrated by comparison of results

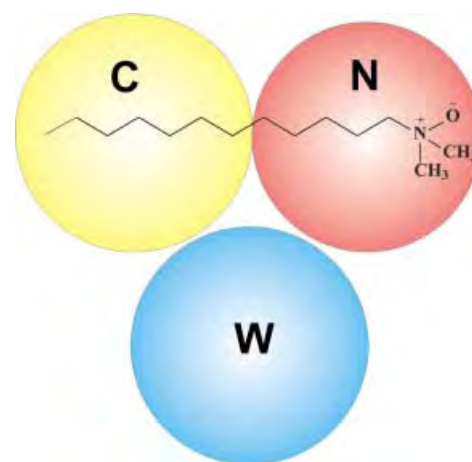


Figure 2. Schematic representation of the simulation model, which shows the fragmentation of the DDAO molecule into two DPD particles. Particles C (yellow) and N (red) are connected together with a harmonic spring. Water is treated as a separate DPD particle W (blue). The calculated repulsion parameters between particles are $a_{C-C} = a_{N-N} = a_{W-W} = 15$, $a_{N-C} = 78$, $a_{N-W} = 0$, $a_{C-W} = 80$.

obtained by computer simulations and experimentally determined phase diagrams of DDAO.^[2]

The building of surfactant mesostructures with the use of classical molecular dynamic simulations at atomic resolution is currently not possible because of the time and length scales at which these phenomena can occur. To date, simulations of micelle structures at the molecular level have been restricted to isolated micelles in aqueous solution.^[3]

The DPD method is a coarse-grained, mesoscale, simulation technique that was introduced by Hoogerbrugge and Koelman.^[4–6] This technique allows the simulation of hydrodynamic behavior in much larger, complex systems, up to the microsecond range. The DPD simulations have been used successfully for calculations of block-copolymer microphase separation and for domain growth and phase separation in binary immiscible fluids.^[7–9] The results of DPD simulations by Jury et al.^[10] have shown that the phase behavior of non-ionic surfactants can be reproduced by this technique.

In DPD the fluid is modeled with soft particles (DPD particles). These particles are not regarded as the molecules of the fluid but rather as droplets or clusters of molecules. The force between each pair of particles is made of a conservative term F^C , a dissipative term F^D , and a random term F^R . The effective force F_i acting on particle i is given by Equation (1).

$$F_i = \sum_{j \neq i} F_{ij}^C + \sum_{j \neq i} F_{ij}^D + \sum_{j \neq i} F_{ij}^R \quad (1)$$

F^D and F^R are responsible for the conservation of total momentum in the system and incorporate the effects of Brownian motion into the larger length scale. The conservative component F^C is regarded as linear up to a cut-off radius r_c , and zero outside of this where r_{ij} is the distance between particles, e_{ij} the unity vector in the direction of the separation, and a_{ij} the interaction parameter between particles i and j [Eq. (2)]. All the forces between the DPD particles are

$$F_{ij}^C = \begin{cases} a_{ij}(1 - r_{ij}/r_c)e_{ij} & (r_{ij} < r_c) \\ 0 & (r_{ij} \geq r_c) \end{cases} \quad (2)$$

[*] Dr. H. Kuhn, E. Ryjkina, Prof. Dr. H. Rehage
Physikalische Chemie
Universität Essen
Universitätsstrasse 3–5, 45141 Essen (Germany)
Fax: (+49) 201-183-3951
E-mail: hubert.kuhn@uni-essen.de
Dr. F. Müller, J. Peggau
Degussa AG
Goldschmidtstrasse 100, 45127 Essen (Germany)

calculated within the constant r_c . The dissipative force F^D depends on the relative particle velocities. F^R provides the energy input in the system which together with the dissipative force, builds a thermostat. The dynamic evolution of the DPD system is governed by Newton's laws.

For the calculation of F^C , the value of a_{ij} must be determined. Here, we have obtained the interaction parameter by the calculation of mean pair contact interaction energy $\langle E_{ij}(T) \rangle$ between DPD particles, that is, between water, or hydrophilic and hydrophobic parts of the surfactant (Figure 2). In the first step, we have calculated the mixing energy of two fragments i and j $E_{\text{Mix}}^{ij}(T)$ according to Equation (3).

$$E_{\text{Mix}}^{ij}(T) = \frac{[Z_{ij}\langle E_{ij}(T) \rangle + Z_{ji}\langle E_{ji}(T) \rangle - Z_{ii}\langle E_{ii}(T) \rangle - Z_{jj}\langle E_{jj}(T) \rangle]}{2} \quad (3)$$

Z_{ii} , Z_{ij} , Z_{ji} , and Z_{jj} are the calculated values of the coordination numbers for each pair of particles. The mean pair-interaction energy $\langle E_{ij}(T) \rangle$ was obtained from Monte Carlo calculations according to Equation (4).

$$\langle E_{ij}(T) \rangle = \frac{\int dE_{ij} P(E_{ij}) E_{ij} \exp\left(\frac{-E_{ij}}{kT}\right)}{\int dE_{ij} P(E_{ij}) \exp\left(\frac{-E_{ij}}{kT}\right)} \quad (4)$$

$P(E_{ij})$ represents the probability distribution of pair-interaction energies. The inter and intramolecular interactions for E_{ij} calculations were calculated with the use of potential functions and parameters of the COMPASS force field. COMPASS is the most recent and accurate force field for the calculation of molecular interactions in aqueous systems. This force field is specifically parameterized for the modeling of fluids.^[11, 12] The Boltzmann distribution of pair interaction energies [Eq. (3)] were generated from calculations of several thousand pairs of different molecular orientations and conformations of molecular fragments. Therefore, the pair-interaction energies were scaled with a temperature function.^[13, 14] Groot and Warren have established a relationship between the Flory–Huggins interactions parameter χ and a_{ij} [Eq. (5a and b)].^[15]

$$a_{ij}(T) = a_{ii} + 3.497\chi(T)^j \quad \text{for } \rho = 3 \quad (5a)$$

$$a_{ij}(T) = a_{ii} + 1.451\chi(T)^j \quad \text{for } \rho = 5 \quad (5b)$$

The a_{ii} terms are derived from the compressibility of pure component i ($a_{ii} = 75 k_B T / \rho$ with density ρ).^[15] For all the simulations presented here, we have set the overall particle density $\rho = N/V$ to the value 5 (in relative units, related to r_c). From the relationship between $E_{\text{Mix}}^{ij}(T)$ (calculated in accordance with Equation (3)) and the Flory–Huggins parameter $\chi^{ij}(T)$ ($\chi^{ij}(T) = E_{\text{Mix}}^{ij}(T)/RT$)^[16] the appropriate repulsion parameter a_{ij} could be defined [Eq. (2)]. In our DPD simulations, we have used the parameters derived from Groot and Warren for the calculations of F_{ij}^D and F_{ij}^R .^[15]

The amphiphilic surfactant molecule DDAO is represented by a dimeric model. The molecule is divided into two types of DPD particle, a hydrophilic particle N ($\text{C}_5\text{H}_{10}\text{N}(\text{CH}_3)_2\text{O}$) and a hydrophobic particle C (C_7H_{15}), which are connected together by a harmonic spring (Figure 2). Water molecules are

represented by the monomer DPD particle W. The dynamics of 40000 DPD particles, starting from random distribution, was simulated in a cubic box under periodical boundary conditions by different surfactant concentrations. For the DPD calculations of phase structures of DDAO, different points have been chosen from an experimentally derived phase diagram,^[2] at defined concentrations.^[17]

Figure 3 shows the experimentally established phase diagram^[2] as well as the calculated stick models (M1, H1, L1) and isodensity profiles (M2, H2, L2) of selected phase structures

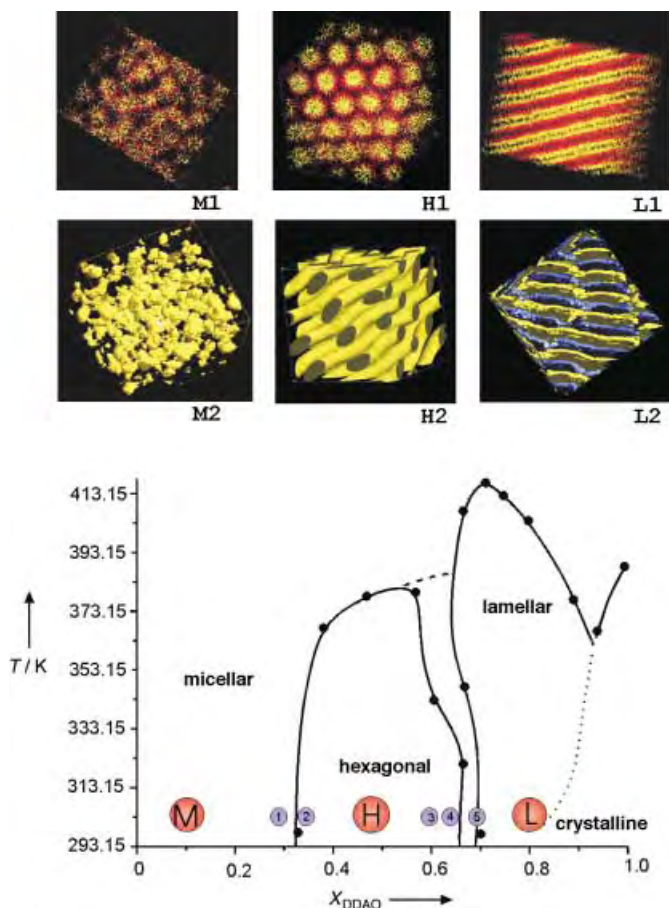


Figure 3. Experimental phase diagram of DDAO water system^[2] with simulated isodensity profiles as well as the stick models of phase structures. M1, M2: micellar phase ($X_{\text{DDAO}} = 0.15$, $T = 303.15$ K); H1, H2: hexagonal phase ($X_{\text{DDAO}} = 0.50$, $T = 303.15$ K); L1, L2: lamella phase ($X_{\text{DDAO}} = 0.80$, $T = 303.15$ K).

in thermodynamic equilibrium. The results of the calculations are in very good agreement with the experimentally observed phase structures. The isotropic micelles (M1, M2) at a surfactant concentration of $X_{\text{DDAO}} = 0.5$ transform into an ordered hexagonal phase (H1, H2). By increasing the concentration of surfactant further to $X_{\text{DDAO}} = 0.8$, a lamellar phase is built (L1, L2). This lamellar phase consists of double membranes comprising surfactant and water layers; the surfactant component consists of two layers of surfactant molecules, the hydrophobic groups of which are aggregated in the middle of the layer. The hydrophilic groups are oriented towards the water. In Figure 3 image L2 shows clearly the

water layers incorporated between the lamellae. The micellar, hexagonal, and lamellar structures can be characterized well by the DPD model.

Figure 4 shows the isodensity surface as well as the stick model of DDAO at the surfactant concentration $X_{\text{DDAO}} = 0.25$ and at $T = 303.15$ K. It can be clearly shown that the concentration increase from $X_{\text{DDAO}} = 0.15$ (M1 and M2 from Figure 3) to $X_{\text{DDAO}} = 0.25$ leads to the building of a more ordered micellar phase with structured micelles.

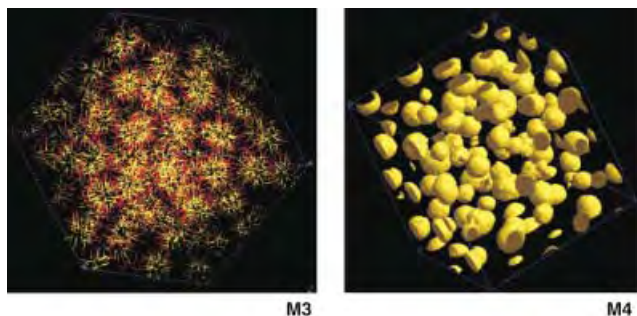


Figure 4. Representation of the micellar phase calculated with DPD at $X_{\text{DDAO}} = 0.25$ and $T = 303.15$ K.

Analysis of the isodensity profiles in sections of the simulation box at $X_{\text{DDAO}} = 0.25$ allows the calculation of the micelle aggregation number $Z_{\text{DPD}} = 71$. This calculated value is in good agreement with the small-angle neutron-scattering measurements (SANS) for DDAO above the cmc in aqueous solutions ($Z_{\text{SANS}} = 78 \pm 2$).^[17]

In the hexagonal phase, highly ordered, rodlike micelles are generated. Figure 5 indicates the progressive development of the hexagonal phase during the simulation. At first a gyroid phase is formed (a, b), which during further progression of the simulation acquires a symmetry, and after 35.7 ns of total time becomes ordered in a hexagonal phase (e, f).

Additional simulations were performed at the regions of phase boundaries. All calculations were performed with $T =$

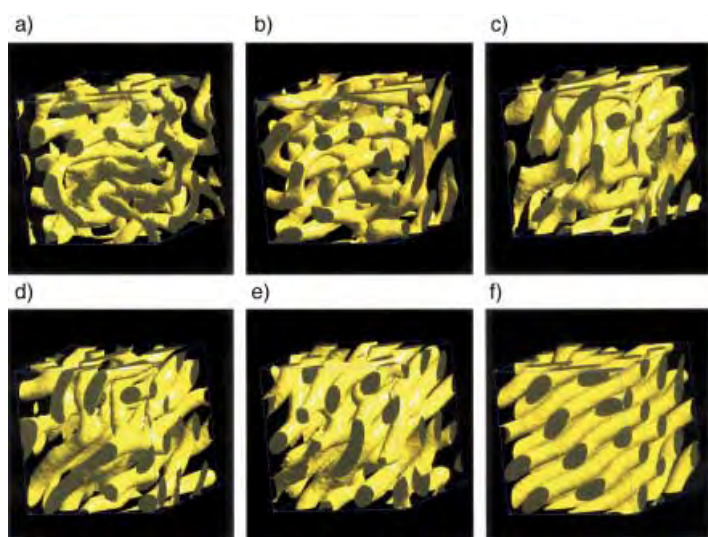


Figure 5. Calculated hexagonal phase ($X_{\text{DDAO}} = 0.50$; $T = 303.15$ K) at different simulation times a) 1.8 ns, b) 9.3 ns, c) 18.6 ns, d) 22.3 ns, e) 27.9 ns, f) 35.7 ns.

303.15 K and for the same time range $\Delta t = 9.3$ ns (50 000 time steps), but at different surfactant concentrations X_{DDAO} . The calculated concentrations are marked with blue points on the experimental phase diagram (Figure 3 ①: $X_{\text{DDAO}} = 0.30$, ②: $X_{\text{DDAO}} = 0.35$, ③: $X_{\text{DDAO}} = 0.60$, ④: $X_{\text{DDAO}} = 0.65$, ⑤: $X_{\text{DDAO}} = 0.70$). The resulting structures are presented in Figure 6. As the Figures indicate, a change in the concentration of 5% in the boundary regions between two phases

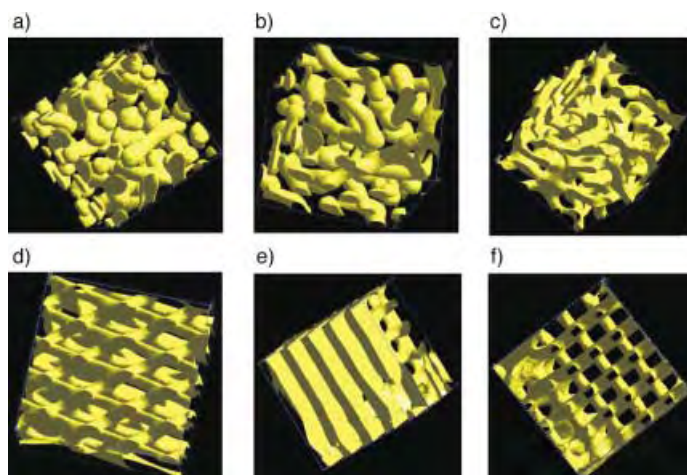


Figure 6. Representation of phase boundary regions with the DPD calculated phases at $T = 303.15$ K and surfactant concentrations: a) $X_{\text{DDAO}} = 0.30$, b) $X_{\text{DDAO}} = 0.35$, c) $X_{\text{DDAO}} = 0.60$, d) $X_{\text{DDAO}} = 0.65$, e) and f) $X_{\text{DDAO}} = 0.70$.

can be reproduced by our DPD calculations. The spherical and rodlike micelles can be seen in Figure 6 a) (①). The gyroid phase in Figure 6 b) (②) and 6 c) (③) becomes ordered into a hexagonal phase during the progression of the simulation. The “viscous isotropic”^[12] phase is shown in Figure 6 d) (④). Figure 6 e) and 6 f) show different perspectives of the structure of phase ⑤. In Figure 6 e) the lamellar formation can be observed, whereas in Figure 6 f), the cubic formation is shown at the opposite site of the simulation box. Therefore, phase ⑤ lies in a phase coexistence region.

The DPD simulation results of a dimer model of the surfactant DDAO introduced in the present work are in very good agreement with experimentally observed phase regions. Future applications of this simulation technique could be valuable for a quick estimation of phase structures of amphiphilic molecules. The calculation effort is comparatively small, since the molecular details as well as intramolecular dynamics are not considered; however, the principal difficulty is the determination of the interaction parameters between the DPD particles.

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A Highly Efficient Catalyst for the Telomerization of 1,3-Dienes with Alcohols: First Synthesis of a Monocarbenepalladium(0)–Olefin Complex**

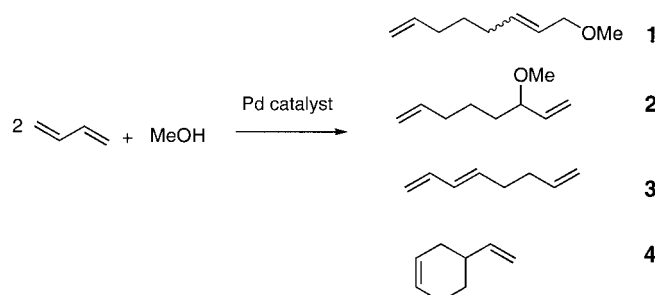
Ralf Jackstell, Mario Gómez Andreu, Anja Frisch, Kumaravel Selvakumar, Alexander Zapf, Holger Klein, Anke Spannenberg, Dirk Röttger, Oliver Briel, Ralf Karch, and Matthias Beller*

Dedicated to Professor Bernhard Lücke on the occasion of his 65th birthday

Some time ago we started a program to develop atom-efficient homogeneous catalytic reactions, which are of interest for the chemical industry, especially the fine chemical industry.^[1] We recently became interested in palladium-catalyzed telomerizations, since these reactions assemble simple starting materials in a 100 % atom-efficient manner.^[2] In general, the telomerization reaction is the dimerization of two molecules of an 1,3-diene in the presence of an

appropriate nucleophile HX, for example, an alcohol,^[3] to give substituted octadienes (1-substituted 2,7-octadiene, 3-substituted 1,7-octadiene). The resulting compounds are useful as intermediates in the total synthesis of several natural products^[4] as well as in industry, as precursors for plasticizer alcohols,^[5] monomers, solvents, corrosion inhibitors, and nonvolatile herbicides.^[6]

Because of their ready availability and their exceedingly low price,^[7] 1,3-butadiene and methanol are the most attractive starting materials for the telomerization reaction (Scheme 1), and yield mainly the 1-substituted 2,7-octadiene



Scheme 1. Products of the telomerization of butadiene with methanol.

1. As previous studies have shown, the major by-products include the 3-substituted octa-1,7-diene (**2**; branched product), 1,3,7-octatriene (**3**; formed by the linear dimerization of butadiene), and 4-vinylcyclohexene (**4**; formed by the Diels–Alder reaction of two molecules of butadiene).

As a result of elegant studies from Jolly^[8] and recent investigations from our side^[9] the mechanism of the palladium-catalyzed telomerization reaction is well-understood. From the catalytic cycle of the reaction it is apparent that one strongly bound and sterically hindered ligand on the palladium center is sufficient to generate a productive and highly selective catalyst system. In fact, in the presence of only one strongly coordinated ligand the activity of the catalyst should be high, because free coordination sites for catalysis are readily available at the metal center.

Therefore, we had the idea that monophosphanepalladium complexes with basic phosphanes should lead to improved catalysts for telomerization reactions. Unfortunately, the tested monophosphanepalladium-1,6-diene^[10] complexes proved not to be superior to the standard palladium/triphenylphosphane catalyst.^[11] Next, we thought that monocarbenepalladium(0) complexes might be more suitable catalysts for our purpose. In the last five years palladium–carbene complexes have become increasingly important as catalysts for Heck-, Suzuki-, and Sonogashira reactions, copolymerizations, and aminations of aryl halides.^[12] However, they have not been reported as catalysts for telomerization reactions.^[13] Despite the increasing interest in this class of complexes, there are only few examples of characterized palladium(0)–carbene complexes known.^[14] To our knowledge there has been no monocarbenepalladium(0) complex without additional phosphane ligands synthesized and characterized. Nevertheless, the synthesis of a monocarbenepalladium(0)–diolefin complex was achieved smoothly by treating the palladium(0)dial-

[*] Prof. Dr. M. Beller, Dr. R. Jackstell, Dr. M. Gómez Andreu, Dipl.-Chem. A. Frisch, Dr. K. Selvakumar, Dr. A. Zapf, Dipl.-Chem. H. Klein, Dr. A. Spannenberg
 Institut für Organische Katalyseforschung an der Universität Rostock e.V. (IfOK)
 Buchbinderstrasse 5–6, 18055 Rostock (Germany)
 Fax: (+49)381-4669324
 E-mail: matthias.beller@ifok.uni-rostock.de

Dr. D. Röttger
 Degussa AG, OXENO C4-Chemie, FEA/PS 1061/14
 Paul-Baumann-Strasse 1, 45764 Marl (Germany)

Dr. O. Briel, Dr. R. Karch
 OMG dmc² division
 Rodenbacher Chaussee 4, 63403 Hanau (Germany)

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yl ether complex $[\text{Pd}_2(\text{dae})_3]^{[15]}$ (dae = diallylether) with 1,3-dimesitylimidazol-2-ylidene carbene (dmi)^[16] in 1,1,3,3-tetramethyl-1,3-divinyl-disiloxane (dvds) at -30°C .^[17a] Crystals of the product 1,3-dimesitylimidazol-2-ylidene-palladium(0) η^2,η^2 -1,1,3,3-tetramethyl-1,3-divinyl-disiloxane ($[(\text{dmi})\text{Pd}^0(\text{dvds})]$; **5**) suitable for X-ray crystallography (Figure 1)^[17b] were obtained by crystallization from pentane at -70°C .

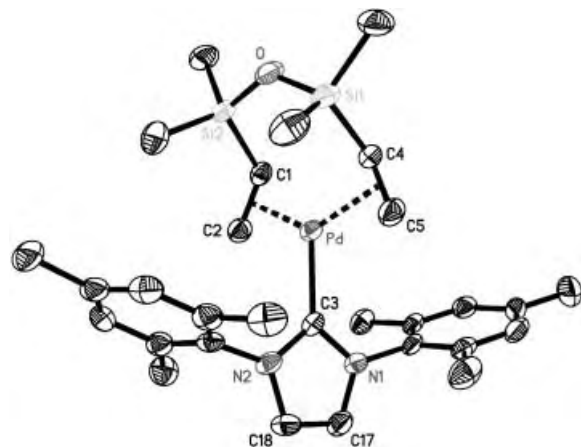


Figure 1. Molecular structure of **5**. The thermal ellipsoids are set at 30% probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: C3–N1 1.373(5), C3–N2 1.369(6), C17–C18 1.320(6), C1–C2 1.408(6), C4–C5 1.388(6), Pd–C3 2.076(5), Pd–C1 2.156(5), Pd–C2 2.137(5), Pd–C4 2.190(5), Pd–C5 2.141(6), N1–C3–N2 102.0(4), N2–C18–C17 106.7(5), N2–C3–Pd 129.3(3), CE1–Pd–CE2 130.3, C3–Pd–CE1 115.3, C3–Pd–CE2 114.3 (CE = mid-points of the coordinated C=C bonds).

The central palladium atom is coordinated by $\text{H}_2\text{C}=\text{CHSiMe}_2\text{OSiMe}_2\text{HC}=\text{CH}_2$ and the carbene ligand (trigonal-planar coordination, Figure 1). The plane of the carbene heterocycle and the coordination plane form an angle of 64.7° . The distance between the palladium center and the carbene atom is 2.076(5) Å, which is in the range found for other palladium–carbene complexes.^[18]

We tested the telomerization of 1,3-butadiene with methanol in the presence of **5**. To be of relevance for practical applications we used comparably small amounts of catalyst (1,3-butadiene:catalyst = 100 000:1 – 300 000:1). Using our previously optimized reaction conditions (90°C , methanol:butadiene = 2:1, 1 mol % NaOH) the former best catalyst system ($\text{Pd}(\text{OAc})_2/3\text{PPh}_3$; **7**) gives a product yield of 79 %, a chemoselectivity of 90 %, and a linear:branched (l:b) ratio of 12:1 (Table 1, entry 1). At 50°C the catalyst is barely active. Using PnBu_3 as the ligand instead of PPh_3 product yield (57 %), and l:b-ratio (10:1) are lower and chemoselectivity is the same (Table 1, entry 4).

The monophosphanepalladium(0)–dvds complex **6**^[10] with a sterically hindered basic phosphane as ligand (PCy_3) is relatively active but comparably low chemoselectivity and l:b ratio are obtained (Table 1, entry 5). In contrast, the monocarbenepalladium(0) complex shows improved catalyst productivity and extremely high selectivity (chemoselectivity = 99 %; l:b = 36:1) giving the desired product in 98 % yield! (Table 1, entry 6). At 50°C there is hardly any other product detected ($\leq 1\%$) apart from the desired diene **1**. Even with a substrate:catalyst ratio of 300 000:1 nearly full conversion is obtained (Table 1, entry 8; catalyst turnover number TON = 267 000). With a further lowering of the catalyst concentration the conversion becomes incomplete. Nevertheless, this is the highest catalyst productivity reported for any telomerization reaction.

Having demonstrated the superiority of **5** in the industrially most important telomerization reaction, we were interested in the coupling of 1,3-butadiene with different alcohols. In general, other alcohols react in the presence of known catalyst systems much less efficiently than methanol and ethanol. In all the reactions the standard conditions as described above were used. The results are summarized in Table 2.

Using aliphatic alcohols the monocarbenepalladium complex **5** is significantly more active and selective than the standard catalyst ($\text{Pd}(\text{OAc})_2/3\text{PPh}_3$). For example using *n*-hexanol and *iso*-propanol in the presence of 0.001 and 0.005 mol % of **5**, respectively, the telomerization products are obtained in 92 and 73 % yield, respectively (Table 2, entries 5 and 7). Applying the same catalyst concentration with the standard catalyst only 1 and 5 % of the corresponding octadienylethers are obtained (Table 2, entry 6 and 8). Also in the presence of phenol as the alcohol the new catalyst proved to be more productive, however, the l:b ratio is lower with **5**, a result which is not understood so far.

In summary, we have synthesized and characterized the first monocarbenepalladium(0)olefin complex. This catalyst shows remarkable productivities and selectivities for a number of telomerization reactions. It is believed that this class of catalysts will be also of use for other palladium-catalyzed coupling reactions. Further studies in this direction, as well as the synthesis of other monocarbenepalladium(0) complexes are in progress.

Table 1. Telomerization of 1,3-butadiene with methanol.^[a]

Entry	Pd cat.	Pd [mol %]	<i>T</i> [°C]	L	Yield [%] ^[b]	Chemoselectivity [%] ^[c]	l:b	TON
1	$\text{Pd}(\text{OAc})_2$	0.001	90	PPh_3	79	90	12:1	78 700
2	$\text{Pd}(\text{OAc})_2$	0.001	50	PPh_3	2	–	13:1	2 000
3	$\text{Pd}(\text{OAc})_2$	0.00033	90	PPh_3	75	88	13:1	225 000
4	$\text{Pd}(\text{OAc})_2$	0.001	90	PnBu_3	57	90	10:1	57 000
5	6	0.001	90	–	60	77	10:1	60 000
6	5	0.001	90	–	≥ 98	99	36:1	98 000
7	5	0.001	50	–	57	> 99	82:1	57 000
8	5	0.00033	90	–	89	98	41:1	267 000

[a] General conditions: 16 h, 90°C , 1 mol % NaOH, MeOH:Butadiene = 2:1, Pd:L = 1:3. [b] Yield of **1** + **2**. [c] Chemoselectivity = $(\mathbf{1} + \mathbf{2})/(\mathbf{1} + \mathbf{2} + \mathbf{3} + \mathbf{4}) \times 100$.

Table 2. Telomerization of 1,3-butadiene with different alcohols.^[a]

Entry	Pd cat.	ROH	Pd [mol %]	Yield [%] ^[b]	Chemoselectivity [%] ^[c]	l:b	TON
1	5	CH ₃ OC ₂ H ₄ OH ^[d]	0.001	97	97	39:1	97 000
2	7	CH ₃ OC ₂ H ₄ OH ^[d]	0.001	35	47	16:1	35 000
3	5	<i>n</i> -C ₄ H ₉ OH ^[e]	0.001	91	96	52:1	91 000
4	7	<i>n</i> -C ₄ H ₉ OH ^[e]	0.001	17	35	16:1	17 000
5	5	<i>n</i> -C ₆ H ₁₃ OH ^[f]	0.001	92	93	37:1	92 000
6	7	<i>n</i> -C ₆ H ₁₃ OH ^[f]	0.001	≤ 1	–	–	–
7	5	<i>i</i> -C ₃ H ₇ OH ^[e]	0.005	73	73	4:1	14 600
8	7	<i>i</i> -C ₃ H ₇ OH ^[e]	0.005	5	11	1:1	1 000
9	5	C ₆ H ₅ OH ^[g]	0.005	56	98	8:1	12 000
10	7	C ₆ H ₅ OH ^[g]	0.005	38	97	19:1	7 600

[a] General conditions: 16 h, 90 °C, 1 mol % Base, ROH:1,3-Butadiene = 2:1, **7** = Pd(OAc)₂/3 PPh₃. [b] Yield of **1** + **b**. [c] Chemoselectivity = (**1** + **b**)/(**1** + **b** + **3** + **4**) × 100. [d] Base: CH₃OC₂H₄ONa. [e] Base: NaOH. [f] Base: *n*-C₆H₁₃ONa. [g] Base: C₆H₅ONa, C₆H₅OH (46 %) in THF.

Experimental Section

General procedure for the telomerization: [(dmi)Pd⁰(dvds)](**5**; 1.6 mg, 2.77 × 10^{−6} mol) was dissolved in methanol (17.8 g, 0.555 mol) under argon (or Pd(OAc)₂ (0.62 mg, 2.77 × 10^{−6} mol) and PPh₃ (2.2 mg, 8.33 × 10^{−6} mol) in the other cases). Then NaOH (111 mg, 2.77 × 10^{−3} mol) was added and the mixture transferred under argon into a secured stainless steel Parr autoclave (100 mL). Then the autoclave was cooled with dry ice. 1,3-butadiene (15 g, 2.77 × 10^{−1} mol) was condensed in a separate pressure cylinder (75 mL, mass control) and this defined amount of 1,3-butadiene was then condensed into the cooled autoclave and the vessel heated to reaction temperature. After the reaction was finished the autoclave was cooled to room temperature and the remaining 1,3-butadiene condensed. *iso*-octane (5 mL) was added as an internal standard. The yield of telomerization products was determined by gas chromatography (GC) by using an HP6869A gas chromatograph. To isolate the different octadienyl ethers the reaction mixture was distilled in vacuo.

cis/trans-**1**: ¹H NMR (CDCl₃, 300 MHz): δ = 1.49 (q, *J* = 8.0 Hz, 2H), 2.68–2.76 (m, 4H), 3.31 (s, 3H), 3.86 (dd, *J* = 6 Hz, *J* = 2 Hz, 2H), 4.95–4.99 (m, 2H), 5.49–5.61 (m, 1H), 5.64–5.87 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ = 27.0, 28.3, 28.7, 31.7, 33.2, 57.6, 57.9, 68.1, 73.2, 114.5, 126.3, 126.4, 133.2, 134.4, 138.5, 138.6.

2: ¹H NMR (CDCl₃, 300 MHz): δ = 1.34–1.68 (m, 4H), 2.01–2.10 (m, 2H), 3.26 (s, 3H), 3.46–3.54 (m, 1H), 4.90–5.20 (m, 2H), 5.14–5.22 (m, 1H), 5.58–5.87 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ = 24.6, 33.7, 34.8, 56.1, 82.9, 114.5, 117.0, 138.7, 138.8.

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- [17] $[\text{Pd}_2(\text{dpe})_2]$ (405 mg, 0.8 mmol) were suspended in 1,1,3,3-tetramethyl-1,3-divinyl-disiloxane (5 mL). The mixture was immediately cooled to -30°C and 1,3-dimesitylimidazol-2-ylidene (340 mg, 1.1 mmol) was added. After warming up to room temperature the solution was stirred for 1 h at this temperature. Then the white complex formed was collected by filtration, washed with pentane (2×5 mL), and dried in vacuo. X-ray structural analysis of **5**: STOE-IPDS diffractometer, graphite monochromatized $\text{MoK}\alpha$ radiation, $\lambda = 0.71069 \text{ \AA}$, structure solved by direct methods (SHELXS-86: G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467) and refined with the full-matrix least-squares method against F^2 (SHELXL-93: G. M. Sheldrick, Göttingen, Germany, **1993**), structural representation: XP (Siemens), $0.4 \times 0.3 \times 0.2$ mm, yellow prism, space group $P2_1/n$, monoclinic, $a = 13.100(3)$, $b = 18.235(4)$, $c = 13.467(3) \text{ \AA}$, $\beta = 105.07(3)^\circ$, $V = 3106.3(12) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calc}} = 1.277 \text{ g cm}^{-3}$, 6157 measured reflections, 3279 were independent of symmetry, of which 2412 were observed ($I > 2\sigma(I)$), $R = 0.033$, $wR2$ (all data) = 0.076, 316 parameters. CCDC-171440 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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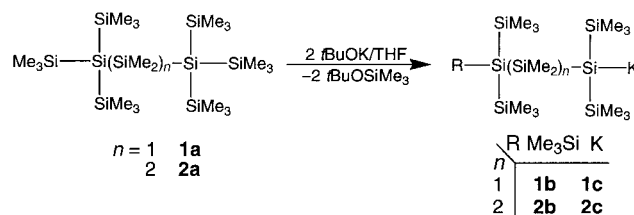
Simple Synthesis of Oligosilyl- α,ω -dipotassium Compounds**

Christian Kayser, Guido Kickelbick, and Christoph Marschner*

The chemistry of electrophilic silicon compounds is a well established and intensively studied area, whereas their nucleophilic counterparts, the so-called silyl anions, enjoyed much less attention for a long time. This is quite astonishing, considering the high popularity of the tris(trimethylsilyl)silyl group, which is mainly introduced through the respective silyl anion, in main group and organometallic chemistry. However, over the last few years this situation has changed and anionic silyl compounds are now the subject of increased investiga-

tions.^[1] Recently, in this context, we have reported the synthesis of oligosilyl anions by cleavage of trimethylsilyl groups with potassium *tert*-butoxide.^[2] This reaction can be regarded as a variation of the method developed by Gilman et al. for the synthesis of oligosilyllithium compounds by cleavage of trimethylsilyl groups with methyllithium.^[3] An advantage of using potassium alkoxides instead of alkyllithium compounds becomes evident in the reaction with higher oligosilanes. In cases where there are additional Si–Si bonds besides the ones between the central silicon atom and the peripheral trimethylsilyl groups, these 'inner' bonds are cleaved exclusively by methyllithium,^[3] whereas potassium *tert*-butoxide selectively removes a trimethylsilyl group.^[2, 4] The access to these higher silyl anions opened the possibility of studying the prospects for the synthesis of multiply metalated oligosilanes.^[4, 5]

Therefore, we treated bis[tris(trimethylsilyl)silyl] compounds, bridged with one (**1a**)^[2, 6] or two (**2a**)^[7] dimethylsilylene units with potassium *tert*-butoxide in THF at elevated temperatures (Scheme 1). Following a fast first metalation step,^[2, 5, 8] the subsequent formation of the dianion takes place more easily when the negative charges are further apart. Whereas the reaction of **2a** to the dianion, occurs at a very low rate, even at room temperature, the conversion of **1a** requires prolonged heating to 60°C .



Scheme 1. Synthesis of mono- and dipotassium compounds.

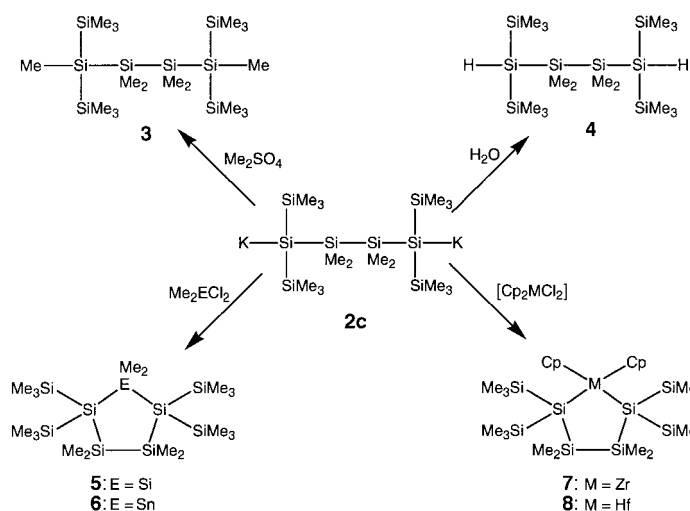
Concerning their reactivity **1c** and especially **2c** behave almost like isolated silyl anions. Derivatization reactions like hydrolysis ($\rightarrow \mathbf{4}$), alkylation with dimethyl sulfate ($\rightarrow \mathbf{3}$)^[9] and the formation of homo- and heterocyclic rings by the reactions with dimethylsilyl ($\rightarrow \mathbf{5}$),^[10] dimethyltin ($\rightarrow \mathbf{6}$),^[11] and metalocene dihalides ($\rightarrow \mathbf{7}$, **8**) proceed very cleanly (Scheme 2). In contrast to what is found for lithium silanides,^[12] the THF molecules of **1b, c** and **2b, c** are not bound very firmly. They can be removed in part in vacuum; therefore, depending on the conditions of isolation a different content of donor molecules can be observed for these compounds.

Control of conversion and characterization of the silyl anions can be achieved most easily by ^{29}Si NMR spectroscopy. The formal exchange of one trimethylsilyl group for a potassium atom results in a shift of the resonance signal of the affected silicon atom of $\Delta\delta \approx 60$ to lower frequencies. At the same time the trimethylsilyl groups in β -position experience a shift of $\Delta\delta \approx 4-5$ in the opposite direction. The second metalation step from **2b** to **2c** effects an additional slight shift of the ^{29}Si resonance signal of the metalated nucleus to lower frequency ($\delta = -192$), which is in accordance with previous observations with alkylidene-bridged dianions.^[5] In contrast to this **1c** exhibits an NMR signal for the metalated silicon

[*] Prof. Dr. C. Marschner, Dr. C. Kayser
Institut für Anorganische Chemie
Technische Universität Graz
Stremayrgasse 16, 8010 Graz (Austria)
Fax: (+43) 316-873-8701
E-mail: marschner@anorg.tu-graz.ac.at

Dr. G. Kickelbick
Institut für Anorganische Chemie
Technische Universität Wien
Getreidemarkt 9/153, 1060 Vienna (Austria)

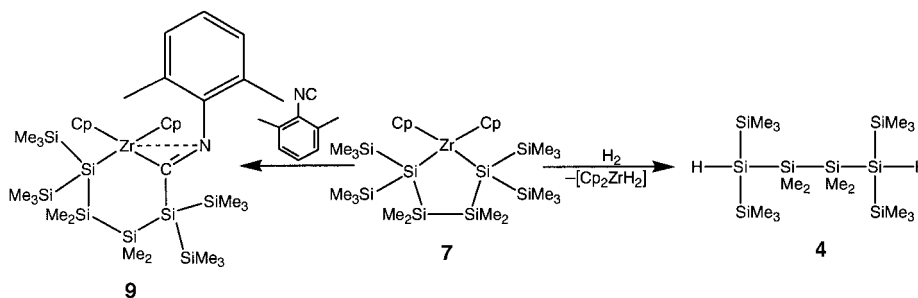
[**] This work was supported by the Austrian science fund (FWF). C. M. thanks the Austrian Academy of Science for an APART fellowship.



Scheme 2. Reactions of **2c**.

atoms at $\delta = -173$. Compared to the resonance of the monometalated compound (**1b**) this corresponds to a shift of $\Delta\delta \approx 15$ to higher frequencies.^[13]

The silyl compounds of the early transition metals can be synthesized most easily by the salt elimination reaction of silyl anions with metal halides.^[14] Because of the limited availability of silyl dianions, early metal compounds with bidentate silyl ligands are only scarcely known.^[15] Therefore, **2c** was tested for its reactivity with zirconocene and hafnocene dichlorides (Scheme 2). The respective reactions proceeded very cleanly to give the expected zirconocena- (**7**) and hafnocenacyclopentasilanes (**8**), which, to the best of our knowledge, are the first examples of these types of compounds.^[15] Both compounds could be characterized unambiguously by single-crystal X-ray structure analysis (Figures 1 and 2).^[16, 17]



Scheme 3. Reactions of **7**.

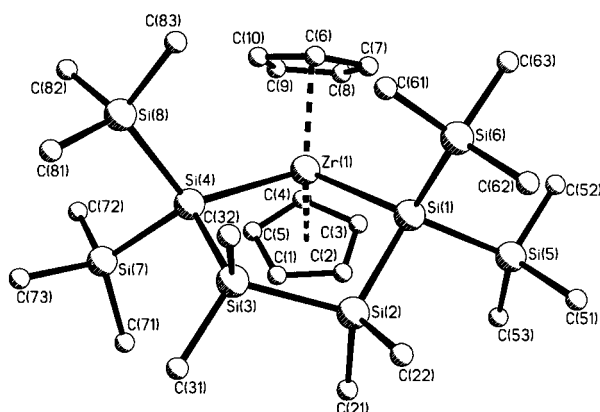


Figure 1. Structure of **7** in the crystal. Selected bond lengths [Å] and angles [°]: Si(1)–Zr(1) 2.8264(19), Si(4)–Zr(1) 2.8497(19), Si(2)–Si(3) 2.351(4), Si(1)–Si(2) 2.387(3), Si(3)–Si(4) 2.378(3), Si(1)–Si(5/6) 2.369(3)/2.376(3), Si(4)–Si(7/8) 2.380(3)/2.386(3), Si(1)–Si(2)–Si(3) 109.25(11), Si(2)–Si(3)–Si(4) 112.79(11), Si(6)–Si(1)–Si(5) 101.42(11), Si(8)–Si(4)–Si(7) 99.46(11), Si(1)–Si(5)–Zr(1) 121.09(9), Si(1)–Zr(1)–Si(4) 97.70(6).

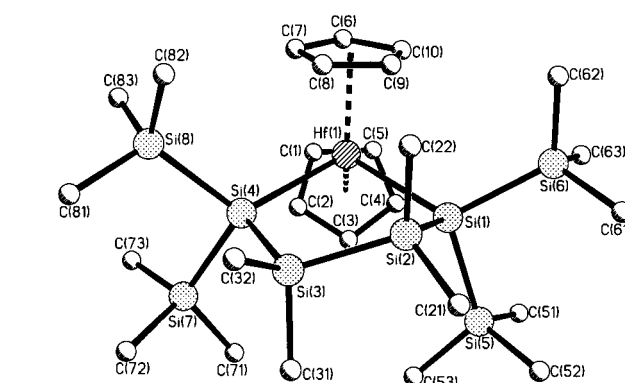


Figure 2. Structure of **8** in the crystal. Selected bond lengths [Å] and angles [°]: Si(1)–Hf(1) 2.791(14), Si(4)–Hf(1) 2.823(15), Si(2)–Si(3) 2.342(3), Si(1)–Si(2) 2.385(2), Si(3)–Si(4) 2.379(2), Si(1)–Si(5/6) 2.374(2)/2.371(3), Si(4)–Si(7/8) 2.382(2)/2.381(2), Si(1)–Si(2)–Si(3) 108.05(9), Si(2)–Si(3)–Si(4) 111.38(9), Si(6)–Si(1)–Si(5) 100.84(9), Si(8)–Si(4)–Si(7) 99.22(9), Si(1)–Si(5)–Hf(1) 119.90(7), Si(1)–Hf(1)–Si(4) 96.41(5).

We oriented our studies of the reactivity of these metalacyclopentanes on work by Tilley et al. on silyl metalocenes,^[18, 19] and carried out reactions with hydrogen, 1-isocyano-2,6-dimethylbenzene, and carbon monoxide. As expected the reaction of **7** with hydrogen led to the quantitative formation of the dihydridometallocene and 1,4-dihydro-1,1,4,4-tetrakis(trimethylsilyl)tetramethylsilane (**4**) (Scheme 3). Reaction of **7** with the isocyanide also proceeded

very cleanly to the insertion product (**9**) (Scheme 3). Even in the presence of excess isocyanide only one insertion step occurs. In contrast to this, reactions of **7** and **8** with CO did not lead to uniform products. However, it could be shown that the first reaction step of insertion of CO into a silicon–metal bond is reversible.^[19a] This reaction is currently under investigation.

Experimental Section

All manipulations were carried out under exclusion of oxygen and moisture, either by conventional Schlenk techniques or through the use of a glove box under a nitrogen atmosphere.

1c, 2c: The starting material (**1a, 2a**; 0.61 mmol) was mixed with two equivalents (0.135 g, 1.22 mmol) of potassium *tert*-butoxide, THF (2 mL) and C_6D_6 (1 mL) were added, and the mixture was heated to 60 °C in a 10-mm NMR tube, either with an attached teflon stop cock or flame sealed. The conversion was monitored by ^{29}Si NMR spectroscopy.

1c: ^1H NMR (300 MHz, THF, C_6D_6 , 25 °C, TMS): δ = 0.91 (s, 6H; $SiMe_2$), 0.51 (s, 36H; $SiMe_3$); ^{13}C NMR (75.4 MHz, THF, C_6D_6 , 25 °C, TMS):

$\delta = 8.50$ (SiMe₃), 2.28 (SiMe₂); ²⁹Si NMR (99.3 MHz, THF, C₆D₆, 25 °C, TMS): $\delta = -5.3$ (SiMe₃), -16.5 (SiMe₂), -172.0 (SiK).

2c: ¹H NMR (500 MHz, THF, C₆D₆, 25 °C, TMS): $\delta = 0.67$ (s, 12H; SiMe₂), 0.57 (s, 36H; SiMe₃); ¹³C-NMR (125.9 MHz, THF, C₆D₆, 25 °C, TMS): $\delta = 8.66$ (SiMe₃), 3.33 (SiMe₂); ²⁹Si NMR (99.3 MHz, THF, C₆D₆, 25 °C, TMS): $\delta = -4.1$ (SiMe₃), -26.7 (SiMe₂), -191.6 (SiK).

7: Zirconocene dichloride (0.50 g, 1.90 mmol, 30% excess) and **2c** (1.46 mmol) were dissolved at room temperature with toluene (5 mL), and the reaction mixture immediately became deep red. After two hours the solvent was removed at reduced pressure, and the residue was dissolved in pentane. After filtration the product was crystallized at -30 °C and obtained as deep red crystals. Yield: 0.90 g (1.30 mmol, 89%). A suitable single crystal was used for an X-ray structure analysis. ¹H NMR (500 MHz, C₆D₆, 25 °C, TMS): $\delta = 6.29$ (s, 10H; Cp-H), 0.45 (s, 12H; SiMe₂), 0.43 (s, 36H; SiMe₃); ¹³C NMR (125.9 MHz, C₆D₆, 25 °C, TMS): $\delta = 108.80$ (Cp), 6.93 (SiMe₃), 2.19 (SiMe₂); ²⁹Si NMR (99.3 MHz, pentane/D₂O capillary, 25 °C, TMS): $\delta = -2.4$ (SiMe₃), -29.2 (SiMe₂), -65.2 (SiZr); elemental analysis (%) calcd for C₂₆H₃₈Si₈Zr (*M_r* = 686.65): C 45.48, H 8.51; found: C 45.01, H 8.47; UV (cyclohexane): λ_{max} (ϵ) = 302 (4000), 466 (800), 556 nm (250).

8: Synthesis and isolation of **8** ([Cp₂HfCl₂] (0.64 g, 1.68 mmol); **2c** (1.28 mmol)) were accomplished analogously to that of **7**. Compound **8** was obtained as deep red crystals in 85% yield (0.84 g; 1.08 mmol), which were suitable for a single crystal X-ray structure analysis. ¹H NMR (500 MHz, C₆D₆, 25 °C, TMS): $\delta = 6.21$ (s, 10H; Cp), 0.49 (s, 12H; SiMe₂), 0.44 (s, 36H; SiMe₃); ¹³C NMR (125.9 MHz, C₆D₆, 25 °C, TMS): $\delta = 108.32$ (Cp), 7.05 (SiMe₃), 2.43 (SiMe₂); ²⁹Si NMR (99.3 MHz, pentane/D₂O capillary, 25 °C, TMS): $\delta = -2.0$ (SiMe₃), -27.8 (SiMe₂), -52.2 (SiHf); elemental analysis (%) calcd for C₂₆H₃₈HfSi₈ (*M_r* = 773.91): C 40.35, H 7.55; found: C 39.79, H 7.56; UV (cyclohexane): λ_{max} (ϵ) = 210 (50000), 344 (3100), 412 (3100), 504 nm (250).

Isonitrile insertion into compound **7**: Compound **7** (0.057 g, 0.08 mmol) was dissolved in C₆D₆ (2 mL) and treated with 1-isocyano-2,6-dimethylbenzene (0.011 g, 0.08 mmol). The initially deep red solution turned orange immediately. NMR spectroscopy showed the exclusive formation of the expected insertions product. Addition of a second equivalent of isonitrile did not lead to another insertion step. The solvent and excess isonitrile were removed in vacuum; the residue was dissolved in pentane and crystallized at -35 °C as yellow crystals. Yield of **9**: 0.030 g (0.04 mmol, 50%). ¹H NMR (500 MHz, C₆D₆, 25 °C, TMS): $\delta = 6.85$ (m, 3H; Ar-H), 5.69 (s, 10H; Cp), 1.94 (s, 6H; Ar-Me), 0.78 (s, 6H; SiMe₂), 0.52 (s, 18H; SiMe₃), 0.51 (s, 6H; SiMe₂), 0.10 (s, 18 H SiMe₃); ¹³C NMR (125.9 MHz, THF, C₆D₆, 25 °C, TMS): $\delta = 279.6$ (C=N), 154.16 (NC_{ar}), 129.56 (C_{ar}), 128.96 (C_{ar}), 128.36 (C_{ar}), 106.46 (Cp), 21.56 (C_{ar}Me), 7.16 (SiMe₃), 4.36 (SiMe₃), 2.16 (SiMe₂), -0.16 (SiMe₂); ²⁹Si NMR (99.3 MHz, pentane/D₂O capillary): -4.36 (SiMe₂), -10.06 (SiMe₃), -33.06 (SiMe₂), -36.36 (SiMe₂), -79.06 (ZrSi), -117.26 (NCSi); elemental analysis (%) calcd for C₃₅H₆₇NSi₈Zr (*M_r* = 817.82): C 51.40, H 8.26; found: C 50.97, H 8.37.

Reactions of **7** and **8** with hydrogen and of **2c** with acid to give dihydrosilane **4**: The respective metallocyclosilane (0.07 mmol) was dissolved in C₆D₆ in an NMR tube. The solution was frozen with liquid nitrogen, evacuated, and flushed with hydrogen. After warming up to ambient temperature the tube was shaken whereupon the red color disappeared. For the isolation of the hydrosilane the solvent was removed in vacuum, the residue dissolved in pentane, and after filtration to remove the insoluble metallocene hydride, the sample was evaporated and the residue **4** crystallized as colorless crystals from acetone. Yield: 0.029 g (0.06 mmol, 85%). Alternatively, **4** was obtained from **2c**, analogously to the previously described hydrolysis procedure with sulfuric acid^[2] in almost quantitative yield. ¹H NMR (500 MHz, C₆D₆, 25 °C, TMS): $\delta = 2.68$ (s, 2H; Si-H), 0.42 (s, 12H; SiMe₂), 0.27 (s, 54H; SiMe₃); ¹³C NMR (125.9 MHz, THF, C₆D₆, 25 °C, TMS): $\delta = 2.47$ (SiMe₃), -1.40 (SiMe₂); ²⁹Si NMR (99.3 MHz, pentane/D₂O capillary): $\delta = -11.1$ (SiMe₃), -36.4 (SiMe₂), -116.4 (Si-H, *J* = 155.9 Hz); MS (70 eV): *m/z* (%): 392 (9) [*M*⁺ - HSiMe₃], 318 (89) [*M*⁺ - H₂SiMe₂], 218 (25) [*M*⁺ - HSi(SiMe₃)₃], 73 (100) [SiMe₃]; elemental analysis (%) calcd for C₁₆H₃₀Si₈ (*M_r* = 467.25) C 41.13, H 10.79; found: C 40.82, H 10.78.

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- [9] Compound **3** was obtained by reaction of **2c** with dimethyl sulfate in toluene at -78 °C in about 85% yield. ¹H NMR (300 MHz, C₆D₆, 20 °C, TMS): $\delta = 0.40$ (s, 12H; SiMe₂), 0.24 (s, 36H; SiMe₃), 0.23 (s, 6H; SiMe); ¹³C NMR (75 MHz, C₆D₆, 20 °C, TMS): $\delta = 1.01$ (SiMe₃), -1.58 (SiMe₂), -11.32 (SiMe); ²⁹Si NMR (59.6 MHz, THF/D₂O capillary, 20 °C, TMS): $\delta = -12.15$ (SiMe₃), -34.80 (SiMe₂), -82.08 (Si(SiMe₃)₃). The same compound was obtained by treatment of (Me₃Si)₂(Me)SiMe₂H with di-*tert*-butyl peroxide: M. Ishikawa, A. Nakamura, M. Kumada, *J. Organomet. Chem.* **1973**, *59*, C11.
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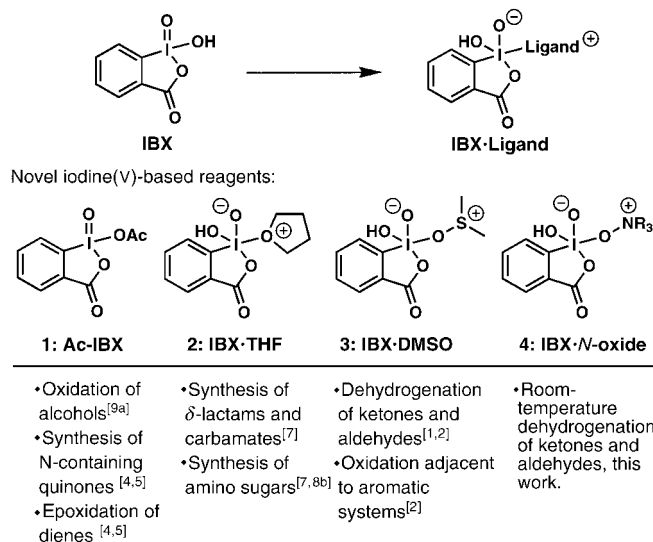
Modulation of the Reactivity Profile of IBX by Ligand Complexation: Ambient Temperature Dehydrogenation of Aldehydes and Ketones to α,β -Unsaturated Carbonyl Compounds**

K. C. Nicolaou,* Tamsyn Montagnon, and Phil S. Baran

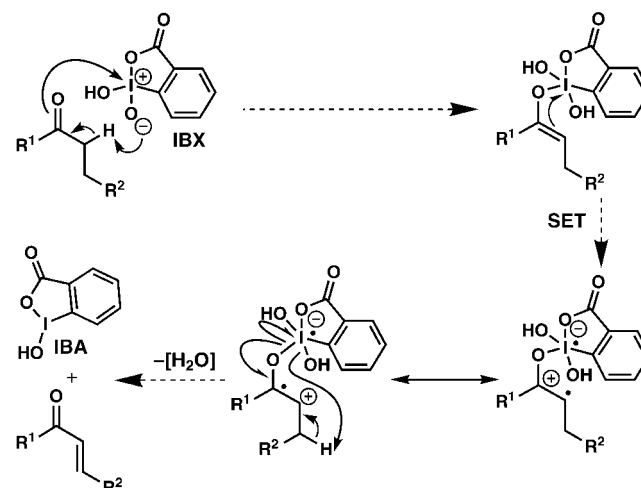
We have recently reported^[1, 2] that the use of IBX (*o*-iodoxybenzoic acid)^[3] represents a highly adept method for accessing the coveted, yet synthetically challenging, α,β -unsaturated carbonyl motif by effecting the dehydrogenation of ketones and aldehydes at elevated temperatures. Our interest^[4–8] in this unique iodine(v) species has grown further owing to the tantalizing discovery that its chemistry can be modulated by complexation with a variety of ligands, thus leading to dramatic changes in its reactivity profile.^[2, 8a, 10] The ligand appended to IBX not only allows moderation of the reagent's reactivity, but also differentiation between reaction pathways when a number of alternatives are available (Scheme 1).^[2] Herein, we report the discovery and elucidation of this new and exciting concept and its application to the

development of a room-temperature dehydrogenation reaction of carbonyl compounds which tolerates a greater breadth of functional groups than previously realized. This development became possible through the introduction of a new class of oxidants, the complexes of IBX with *N*-oxides (4, Scheme 1), which often exhibit superior reactivity to that of the parent reagent.

Extensive investigations^[2] into the original IBX-mediated dehydrogenation reaction demonstrated that at elevated temperatures, IBX dissolved in DMSO acted as a single electron transfer (SET) agent and as such effected oxidation adjacent to carbonyl functionalities to furnish their α,β -unsaturated counterparts (Scheme 2). On a number of



Scheme 1. Access to, and reactivity of novel iodine(v)-based reagents formed by complexation of IBX with different ligands.



Scheme 2. Postulated mechanism for the IBX-mediated dehydrogenation of ketones and aldehydes to α,β -unsaturated carbonyl compounds.

occasions, however, when these reactions were performed in deuterated DMSO and monitored by means of ¹H NMR spectroscopy, unexpected signals were observed which we surmised could derive from a complex between DMSO and IBX (3, Scheme 2). Because these observations were made only in samples that had been subjected to heating at > 50 °C, and since our procedure to dehydrogenate carbonyl species required elevated temperatures, we speculated that it might be a complex of IBX and DMSO that was the active agent in these oxidation reactions. We were, therefore, pleased to find that heating IBX in DMSO at 75 °C for 30 min provided a solution, which upon cooling to 25 °C could indeed effect limited dehydrogenation of a test substrate, cyclooctanone (5, see Figure 1, trace d). The conversion after this activation process was greater than that observed in a parallel experiment with IBX that had merely been dissolved in DMSO at room temperature (Figure 1, trace e). With these promising results in hand, the search for other IBX complexes with improved reactivity was immediately initiated.

A number of well-characterized complexes of IBX with hydroxy and 1,2-dihydroxy compounds and IBX analogues have been reported in the literature,^[9b] having been observed during studies into the Dess-Martin periodinane (DMP)- and IBX-mediated oxidation of alcohols. Furthermore, we were mindful of the dramatic effect that a switch in reaction media

[*] Prof. Dr. K. C. Nicolaou, Dr. T. Montagnon, Dr. P. S. Baran
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

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produced during our forays into the IBX-mediated cyclization or oxidation of multifunctionalized molecules and the importance of solvent (THF) coordination in this instance.^[2, 8a] We surmised, however, that heteroatom oxide ligands (e.g. DMSO), when appended to IBX, might provide a unique electronic environment around the iodine center which could enhance the propensity of these reagents to serve as electron sinks. As such, we focused our first study on this category of potential ligands; the results are illustrated in Figure 1.^[11]

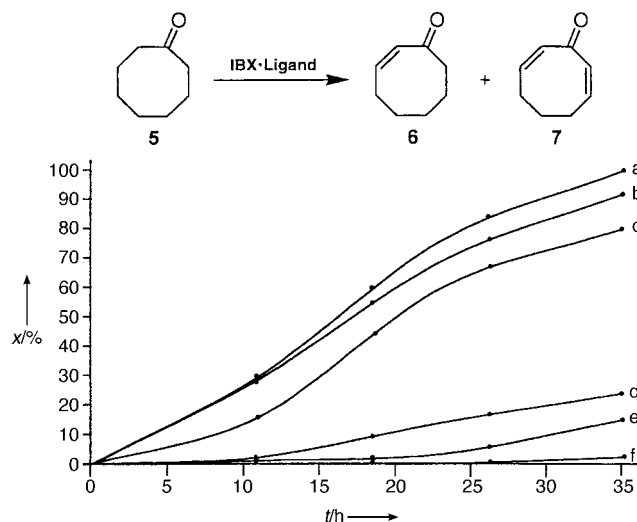


Figure 1. Graph of the rate of conversion of cyclooctanone (5) into dehydrogenated products (*cis* enone 6 and dienone 7) over time, for different IBX·ligand systems: a) IBX·MPO; b) IBX·NMO; c) IBX·trimethylamine-*N*-oxide; d) IBX·DMSO formed by dissolution at 75 °C for 30 min; e) IBX·DMSO formed by dissolution at 25 °C; f) IBX·DMSO formed by dissolution at 90 °C for 20 min (leads to significant quantities of IBA from the reduction of IBX by DMSO which inhibits the desired reaction^[2]). Reagents and conditions: IBX/ligand 1:1 (2.2 equiv), [D₆]DMSO, 25 °C, conversion monitored by means of ¹H NMR spectroscopy. x = Total dehydrogenation.

The formation of a distinct complex was most easily detected in the case of *N*-methylmorpholine-*N*-oxide (NMO). Thus, when NMO and IBX (1:1) were dissolved in deuterated DMSO at room temperature, 100 % conversion into a complex was clearly observed (¹H and ¹³C NMR spectroscopy, see Figure 2).

The most gratifying result to emerge from this initial survey of potential ligands was observed with 4-methoxypyridine-*N*-oxide (MPO), which resulted in the clean and effective conversion of cyclooctanone (5) into the dehydrogenated products (6 and 7, Figure 1, trace a). The success of this ligand relative to other *N*-oxides^[11] can be rationalized as resulting from two key features of MPO: mesomeric stabilization of the positive charge by the methoxy substituent, and the inclusion of the *N*-oxide moiety on the aromatic nucleus, thus preventing oxidative degradation of the ligand under the reaction conditions. Subsequent experimentation demonstrated that this complex, when employed in the dehydrogenation reaction of carbonyl substrates, is not only general but also mild and highly efficient (see Table 1). However, for optimal results, certain conditions must be fulfilled, particularly with

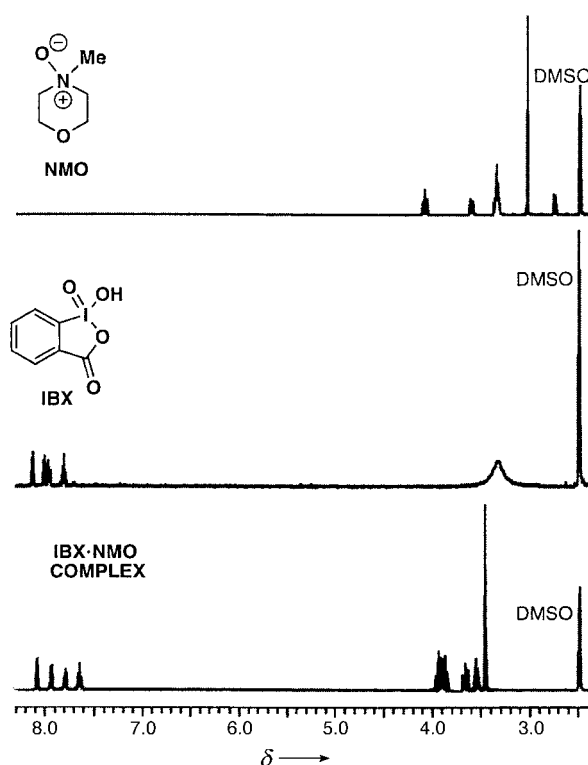


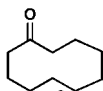
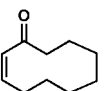
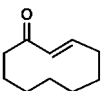
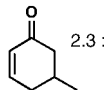
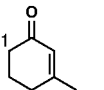
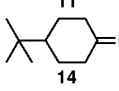
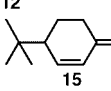
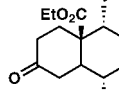
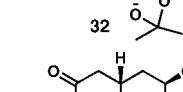
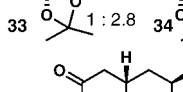
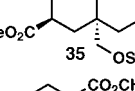
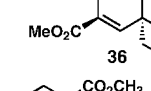
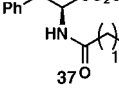
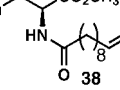
Figure 2. ¹H NMR spectra (500 MHz, [D₆]DMSO) of NMO (top), IBX (center), and the observed NMO·IBX complex (bottom).

respect to the quality of IBX, the concentration, and the substrate solubility (see Table 2 and Experimental Section).

Substrates that previously did not lead to products in satisfactory yields for a variety of reasons, perform well under the present conditions (Table 1, entries 8, 10, 12, and 17). Thus, the advantages of this method are particularly apparent with acid-labile substrates and in cases in which β-elimination is possible. Furthermore, the first productive example of the inclusion of an alkyl amine in a substrate subjected to IBX-mediated dehydrogenation was observed (Table 1, entry 17). The success of the reaction of this challenging substrate can be attributed directly to the lower temperature employed, since substrates with an amine functionality decompose readily when exposed to IBX at elevated temperatures. The IBX·MPO complex is the reagent of choice for the dehydrogenation of reactive or volatile aldehydes, because the method is particularly efficient and mild, and minimal purification is required (Table 1, entries 5–8). Furthermore, other IBX-induced SET reactions^[2, 8a] such as benzylic oxidations^[8c] do not compete with carbonyl dehydrogenation (Table 1, entries 15 and 16).

In conclusion, we have unearthed new details about the nature of the oxidant in the IBX-mediated dehydrogenation of carbonyl compounds originally discovered in these laboratories^[1, 2] which suggest that the active species in this reaction is most likely a complex between IBX and DMSO. By using insight gained in the rational design of new oxidants, IBX·MPO was developed as an effective dehydrogenation reagent for carbonyl compounds and exhibits high selectivity under remarkably mild conditions. The precise origins of the accelerating effect induced by the *N*-oxide complexes 4 in this

Table 1. Facile room temperature dehydrogenation of ketones and aldehydes using IBX · MPO.^[a]

Entry	Substrate	Product(s)	Conditions		Yield [%] ^[b]
			IBX · MPO [equiv]	t [h]	
1			3.5	18	96
2		 2.6 : 1 	1.8	24	78
3		 2.3 : 1 	2.5	32	79
4			1.8	36	86
5			2.2	22	84
6			4.0	48	78 ^[c]
7			2.5	30	88
8		 1 : 1.32 	1.4	42	72
9			1.8	20	77
10			2.5	24	74
11			2.2	32	92
12			1.8	40	81
13		 1 : 2.8 	2.2	48	78
14			1.5	15	91
15			1.5	15	88
16			3.0	45	43 ^[e]
17			2.2	48	62 ^[f]

[a] Reactions were carried out on a 0.1–1.0 mmol scale in DMSO. [b] Yield of isolated chromatographically pure compound. Some starting material was always recovered; however, the quantity is only specified when it exceeds 20 %. [c] Plus 11 % enone. [d] Plus 21 % recovered starting material. [e] Plus 37 % recovered starting material. [f] Plus 34 % recovered starting material. MPO = 4-methoxypyridine-*N*-oxide; SEM = 2-(trimethylsilyl)ethoxymethyl; Bn = benzyl; TBS = *tert*-butyldimethylsilyl.

Table 2. Effect of concentration and solvent composition on the outcome of the IBX·MPO-mediated dehydrogenation reaction.^[a]

Entry	Substrate (M)	Solvent	IBX·MPO [equiv]	Time [h]	Yield [%] ^[b]
1	35 (0.20)	DMSO	1.5	15	0
2	35 (0.20)	DMSO/THF (1:1)	1.5	15	<40
3	35 (0.20)	DMSO/CH ₂ Cl ₂ (2:1)	1.5	6	92
4	35 (0.20)	DMSO/CH ₂ Cl ₂ (1:1)	1.5	15	91
5	14 (0.40)	DMSO	2.0	40	68
6	14 (0.50)	DMSO	2.0	40	72
7	14 (0.75)	DMSO	2.0	40	87
8	16 (0.36)	DMSO	2.2	22	82
9	16 (0.48)	DMSO	2.2	22	76
10	16 (0.55)	DMSO	2.2	22	73
11	16 (0.55)	DMSO/CH ₂ Cl ₂ (2:1)	2.2	22	86

[a] Reactions were carried out on a 1.0 mmol scale. [b] Yield of isolated chromatographically pure compound.

dehydrogenation reaction is the subject of continuing research. Elucidation of these features should facilitate further rational designs toward expanding this new area of chemistry whose applications in organic synthesis are expected to be widespread. These results introduce a new paradigm for modifying the iodine(v) nucleus and, hence, controlling its reactivity profile.

Experimental Section

IBX (1.2 mmol) and MPO^[12] (1.2 mmol) were added to DMSO (see Table 2 for concentration effect) and stirred at ambient temperature until complete dissolution (15–60 min). The carbonyl compound (0.5 mmol) was added, and the mixture was stirred vigorously at the same temperature. The reaction progress was monitored by thin-layer chromatography. The reaction mixture was diluted with an equal volume of aqueous NaHCO₃ (5%) solution and extracted with diethyl ether (3 ×). The combined organic phase was filtered through a pad of celite and then washed with saturated NaHCO₃ solution, water, and brine. After drying (MgSO₄), the organic layer was concentrated to yield the crude product, which could be further purified by column chromatography (silica gel).

For optimal results in this reaction the following points should be noted: a) in cases in which the substrate was not soluble in the DMSO solution of IBX·MPO, increasing amounts of CH₂Cl₂^[13] were added as co-solvent until dissolution, and/or the rate was optimized (see Table 2); b) a large excess of IBX·MPO complex is not recommended, as the rather insoluble IBA formed under these conditions causes precipitation of IBX; in this respect it is also important that the IBX quality is assured by preparation in strict accordance to the method of Santagostino^[14] and subsequent checking by means of ¹H NMR spectroscopy; c) commercial DMSO (Aldrich) was used directly without prior drying; furthermore, it was noted that anhydrous solvent (sequential drying over activated 4-Å molecular sieves) was deleterious to the yield; d) IBX is light-sensitive, thus the reaction vessel was covered with aluminum foil.^[15]

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- [11] In addition to the ligands shown in Figure 1, *n*Bu₃P=O, *t*BuOH, 2-picoline-*N*-oxide, and 4-phenylpyridine-*N*-oxide were examined, but the rate of reaction for these complexes was lower than that of uncomplexed IBX under the same conditions.
- [12] The commercially available hydrate of MPO, which is considerably less hygroscopic than NMO, was used. The IBX·NMO complex is prepared in the same manner and can also be successfully employed at ambient temperature, although the reaction times are longer and the yields show greater variation with this reagent.
- [13] When CH₂Cl₂ is used as cosolvent the reaction rate is retarded; however, its addition was frequently necessary to obtain complete solubility of the substrate (see Table 2, entries 1–4).
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Oxidation of Silyl Enol Ethers by Using IBX and IBX·*N*-Oxide Complexes: A Mild and Selective Reaction for the Synthesis of Enones**

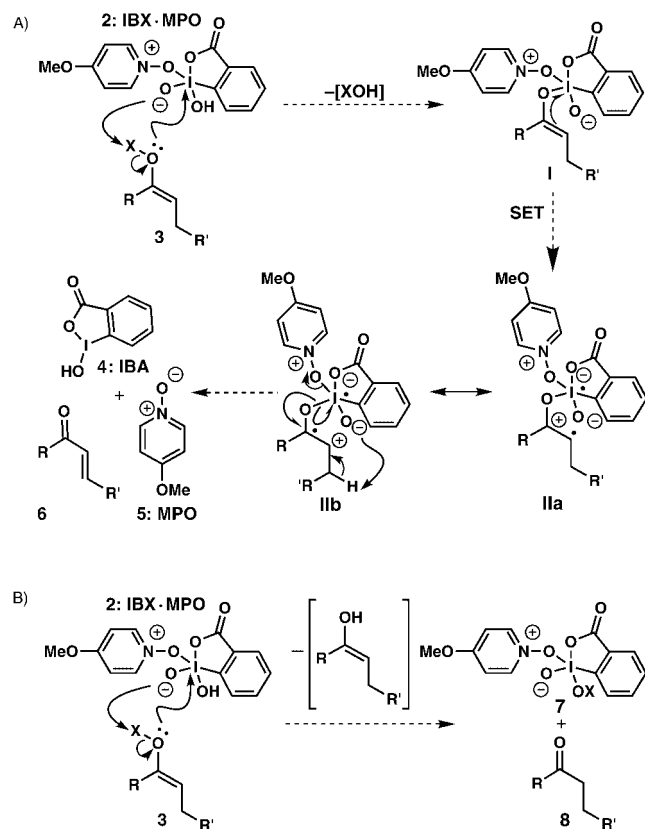
K. C. Nicolaou,* David L. F. Gray, Tamsyn Montagnon, and Scott T. Harrison

Our recent explorations into the chemistry of iodine(v) reagents have highlighted their remarkable synthetic utility.^[1–8] In particular, IBX (*o*-iodoxybenzoic acid) has proved to have a rather unique set of properties which can be appropriately exploited to manipulate the course of a reaction.^[7,9] In the preceding paper,^[9] we delineated the

[*] Prof. Dr. K. C. Nicolaou, D. L. F. Gray, Dr. T. Montagnon, S. T. Harrison
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

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discovery and evolution of IBX·N-oxide complexes and their use in the dehydrogenation of ketones and aldehydes at ambient temperature.^[9] We have postulated that these IBX-mediated dehydrogenation reactions^[4,7,9] proceed through enolization (facilitated by the reagent) with concomitant capture of the enolate moiety, followed by single electron transfer (SET) to IBX and rearrangement of the resulting radical cation to give the α,β -unsaturated carbonyl compound.^[7] This assessment led us to speculate that silyl enol ethers might undergo a similar oxidation with IBX, which would be a new, complimentary oxidation method for the synthesis of the much coveted enone functionality (Scheme 1 A). Herein we report the successful implementation



Scheme 1. Proposed mechanism for A) dehydrogenation, or B) ketone formation, from enol ethers with the IBX·MPO complex.

of this strategy in the conversion of a diverse set of ketones into their α,β -unsaturated counterparts by the fast oxidation of the corresponding TMS enol ethers (for abbreviations, see legends in schemes) induced by IBX (1) or the IBX·MPO complex (2, Figure 1).^[9] We also describe the extension of this powerful method to cascade sequences that involve tandem conjugate additions of organometallic reagents to enones, trapping of the resultant enolates, and regeneration of the original enone motif, thereby increasing the molecular complexity without sacrificing functionality.

The oxidation of silyl enol ethers to enones has frequently been used in the construction of complex molecules, and the multiplicity of protocols available attests not only to its versatility but also to deficiencies in the known methodology

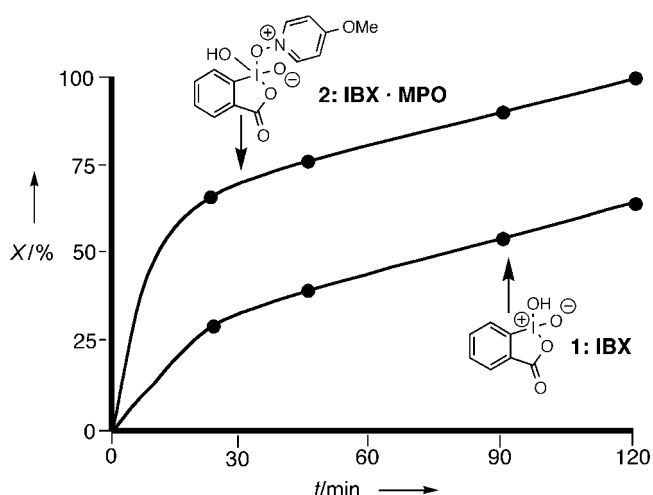


Figure 1. Graph of the rate of conversion of the TMS enol ether derived from cyclooctanone (31), to cyclooctenone (32) by using IBX (1) or IBX·MPO complex (2).^[29] X = Conversion of TMS enol ether into cyclooctenone (32).

for its implementation.^[10–16] Amongst the known procedures for this transformation, the palladium-catalyzed protocol,^[15, 16] originally introduced by Saegusa and co-workers,^[15] stands out by virtue of its relative efficiency and mild nature. However, even within this preferred method, a great variation is seen in the reaction conditions, in the catalyst employed and, ultimately, in the yields of product. These disadvantages, when added to the expense associated with the use of palladium and its incompatibility with various functional groups, allow considerable room for improvement in this area. As our investigations with hypervalent iodine(v) reagents evolved, it was gratifying to discover the remarkable ease with which IBX-based reagents, particularly the IBX·MPO complex (2, Figure 1), converted TMS enol ethers into α,β -unsaturated carbonyl compounds.

As shown in Table 1, a wide variety of sensitive functionalities can be tolerated under the employed conditions; the reaction times are short, and the yields are often very high. Thus, substrates that contain reactive functionalities, for example, amines, sulfides, mesylates, TBS ethers, dithianes, or primary iodides (Table 1, entries 2, 3, 6, 9, 12, and 13) all furnished the desired enones in high yield. Significantly, the protocol works well in a number of situations which caused problems with known methods. For example, generation of allylic epoxide 30 proceeds in high yield (Table 1, entry 10) and a proximal, but unconjugated olefin in the product 26 (Table 1, entry 8) remains unaffected under these conditions. Furthermore, a survey of the literature^[17–19] revealed that the oxidation of indanones to form indenones is frequently cumbersome or can be plagued by low yields or multiple by-products. In contrast, the current method performs admirably well in this challenging situation (Table 1, entries 4 and 5), and furnishes the corresponding enones in yields that significantly exceed those obtained by the best published procedure (< 75%), which involves the use of a stoichiometric amount of Pd(OAc)₂ to oxidize the silyl enol ether.^[19] Although the oxidation of cyclooctanone (31; Table 1, entry 11) may appear trivial, this specific ring size, and hence strain, leads to a lack

Table 1. Facile room temperature dehydrogenation of ketones via the corresponding trimethylsilyl enol ethers by using IBX·MPO complex.^[a]

Entry	Substrate	Product	TMS enol ether formation ^[b]	IBX·MPO [equiv]	Time [min]	Yield [%] ^[c]
1			A	1.5	40	96
2			A	1.5	40	92
3			A	1.5	40	88
4			A	1.3	40	94
5			A	1.5	30	95
6			C	3.0	240	72 ^[d]
7			B	1.5	60	94 ^[e]
8			1 : 5 : 3			
9			A	1.5	40	94
10			C	1.5	60	62 ^[f]
11			C	1.5	40	93
12			A	1.1	20	96
13			C	4.0	360	43 ^[g]
14			C	2.0	120	76

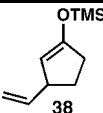
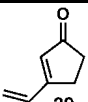
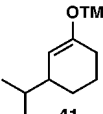
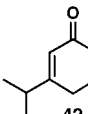
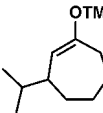
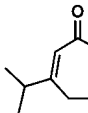
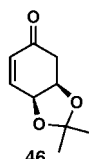
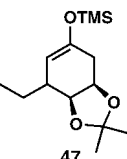
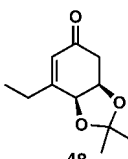
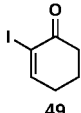
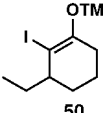
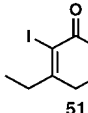
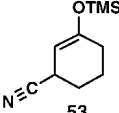
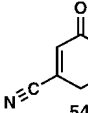
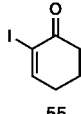
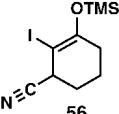
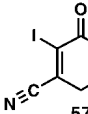
[a] Reactions were carried out on a 0.1–5.0 mmol scale in DMSO/CH₂Cl₂ (see main text for discussion). [b] A: ref. [20], B: ref. [21], C: ref. [22]. [c] Yield of isolated chromatographically pure compound, except where stated. The starting ketone was frequently recovered as the product of enol ether hydrolysis but is only noted when > 10%. [d] Plus 23% inseparable ketone, ratio assigned by means of ¹H NMR spectroscopy. [e] Product distribution assigned by means of ¹H NMR spectroscopy. [f] Plus 33% ketone. [g] Plus 52% inseparable ketone, ratio assigned by means of ¹H NMR spectroscopy. MPO = 4-methoxypyridine-*N*-oxide.

of specificity in the alternate IBX methodologies,^[7,9] in which the dienone is a major component of the product mixture. However, the present method allows for the introduction of just one double bond through the formation of the silyl enol ether, followed by oxidation with **2**.

The method is not without limitations, as substituents at the α position of the ketone substrate lead to some complications, including the regioselective generation of the silyl enol ether, an issue which is amply covered in the literature.^[20–22] In the simplest case of α substitution that we examined (Table 1, entry 7) the oxidation reaction is essentially nonselective (*exolendo* ca. 5:3). With compounds that bear a phenyl group at the α position, the desired oxidation reaction was unfeasible as a result of the propensity of the highly stabilized incipient radical cation (e.g. **IIa**, Scheme 1 A) to dimerize. The influence of steric hindrance around the carbonyl group could not be easily evaluated owing to the difficulties in accessing a range of α -substituted substrates (see above). However, an adjacent tertiary center (Table 1, entry 9) and an iodine atom (Table 2, entries 5 and 7) are both well tolerated. In a number of examples (e.g. Table 1, entries 6, 9, and 12), the alternate reaction pathway, that is, hydrolysis of the silyl enol ether back to the original starting ketone (Scheme 1 B), proved to be of greater significance. There are generally two reasons for this observed side reaction. First, the insolubility of the substrate in DMSO, such as with a steroid-derived enol ether (Table 1, entry 9), which required the addition of a large volume of CH_2Cl_2 , thus leading to a slower oxidation reaction and competing hydrolysis.^[23] In the enol ethers derived from substrates **19**, **33**, and **35** (Table 1, entries 6, 12, and 13) coordination to the oxidant through heteroatoms may be responsible for the need to use excess IBX, thus leading to the retardation of the desired reaction and varying degrees of competing hydrolysis. The second reason relates to the reactivity of the silyl enol ether (Table 2, entry 1). Thus, when highly reactive species were utilized, hydrolysis was rapid (even beginning upon isolation of the enol ether), and oxidation was compromised. This result precluded the inclusion of silyl ketene acetals as substrates for this method.

Incorporation of the current oxidation method within a cascade reaction could allow a rapid increase in molecular complexity. Particularly attractive appeared to be a sequence that involved conjugate addition to an enone, followed by in situ silyl enol ether formation, and subsequent isolation and oxidation of the resulting product to regenerate a new enone functionality for further elaboration. Table 2 summarizes the results of the implementation of this strategy. Thus, the addition of cuprate reagents (RMgX , $\text{CuBr} \cdot \text{SMe}_2$) to enones **37**, **40**, **43**, and **46** (Table 2, entries 1–4) followed by quenching with TMSCl and oxidation of the resulting silyl enol ethers with IBX (**1**) or IBX·MPO (**2**) furnished the elaborated enones **39**, **42**, **45**, and **48**, respectively, in high overall yields. Some of these products were difficult to synthesize by means of alternative protocols.^[24] This is particularly true for the sensitive enone product **48**, which was difficult to obtain from the corresponding saturated ketone. This protocol was extended to the synthesis of enones substituted at the α -position with iodine (Table 2, entries 5 and 7) and at the β

Table 2. Dehydrogenation of trimethylsilyl enol ethers, formed in situ from an enone.^[a]

Entry	Substrate	Silyl enol ether	Product	Yield [%] ^[b]
1				90 ^[c]
2				97 ^[d]
3				94
4				47 ^[c,d]
5				98
6				98
7				82 ^[c]

[a] Reactions were carried out on a 2.0 mmol scale. [b] Overall yield of pure isolated compound, no chromatography required. [c] Chromatography required to separate enone from hydrolysis product. [d] Oxidation performed without complex, IBX (1.5–2.0 equiv) added as a solid to a solution of enol ether in DMSO (see 2 below). Reagents and conditions: Entries 1–5; 1) $\text{CuBr} \cdot \text{SMe}_2$ (2.0 equiv), THF, -78°C add RMgX (4.0 equiv), 30 min; then add TMEDA (4.0 equiv), TMSCl (5.0 equiv), enone (1.0 equiv) in THF, $-78 \rightarrow 25^\circ\text{C}$, 30 min. Entries 6 and 7; 1) Et_2AlCN (1.3 equiv), hexanes, -10°C , add enone, 90 min; then pyridine (4.0 equiv), TMSCl (3.7 equiv), $-10 \rightarrow 25^\circ\text{C}$, 2 h. 2) Add preformed solution of IBX·MPO complex (1.5–2.0 equiv, 0.4 M in DMSO) to substrate, vigorous stirring, 30–60 min. TMS = trimethylsilyl. TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

position with cyanide (Table 2, entries 6 and 7) by the use of Et_2AlCN .^[25]

IBX (**1**) and IBX·MPO complex (**2**) were examined in their reactions with a range of enol ethers derived from cyclohexanone (Table 3). Only the TBS enol ether **58c** was inert to the reaction conditions, as all the remaining substrates led to ketone **59** and/or enone **60** as products. The extent to which the enone arose from the complex-mediated dehydrogenation of the corresponding saturated ketone^[9] was not significant, although it was found to be dependent on the substrate. The oxidation of the TES enol ether **58b** was, as predicted, slower than that of the TMS enol ether **58a**. When the TES enol ether was used in more sophisticated examples

Table 3. Reactions of various enol ether derivatives of cyclohexanone with IBX · MPO complex.

Enol ether 58	X	58	59	60	Time [h]
a:	TMS	0	0	1	1
b:	TES	0	1	18	8
c:	TBS	1	0	0	12
d:	Ac	8	1	0	12
e:	Me	3	6	1	2
f:	CH ₂ CH=CH ₂	3	8	1	1

[a] see main text for discussion. [b] Ratios determined by ¹H NMR spectroscopy.

such as steroid **27** and amine **33** (Table 1, entries 9 and 12), no significant dehydrogenation occurred, with hydrolysis being the major pathway. The ease with which IBX effects hydrolysis of the relatively stubborn **58e** may be readily rationalized by the mechanism shown in Scheme 1B, since both the Lewis acidity and nucleophilicity of IBX are well known.^[26] We propose that the oxidation reaction of TMS enol ethers is likely to proceed through a SET pathway by analogy to the original IBX-based method (Scheme 1A).^[7]

In conclusion, we have developed an extremely mild and efficient procedure for the oxidation of silyl enol ethers to the corresponding α,β -unsaturated carbonyl compounds through the use of IBX (**1**) or its MPO complex **2**, which is complimentary to the method delineated in the preceding paper.^[9] By careful selection of one of these two protocols, based on the substrate features, a diverse set of carbonyl compounds can now be dehydrogenated with ease. This method exhibits a broad scope, affords clean products in high yields, and is expected to find wide-ranging applications in organic synthesis.

Experimental Section

Typical procedure: IBX^[27] and MPO^[28] (1.1 to 4.0 equiv) were dissolved in DMSO (0.4M) in an equimolar ratio at ambient temperature. The solvent used was not dried, and no precautions were taken to exclude moisture or oxygen from the reaction vessel. The TMS enol ether was generated by using one of a number of established procedures (depending on the substrate) from the carbonyl compound (1.0 equiv).^[20–22] The crude TMS enol ether was vacuum-dried wherever possible to minimize the amount of (TMS)₂O present, as this was detrimental to the desired reaction. The IBX · MPO solution was added in one portion at ambient temperature to the crude TMS enol ether dissolved in a minimum of DMSO. In cases in which the substrate was not completely soluble in DMSO, CH₂Cl₂ was added dropwise to the suspension (or emulsion) until clear. The CH₂Cl₂ content was always minimized, as its use as a cosolvent retards the reaction.^[4, 23] The solution was stirred vigorously, and progress was monitored by means of thin-layer chromatography. Upon completion, the reaction mixture was diluted with aqueous NaHCO₃ (5 %) and extracted with diethyl ether (3 ×). The combined organic phase was filtered through a pad of celite and washed with saturated aqueous NaHCO₃, water, and brine. After drying (MgSO₄), the solvent was removed in vacuo to yield the crude product, which could be purified further by means of column chromatography.

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- [29] In this case, the reaction was carried out at higher dilution to give a timescale appropriate for accurate monitoring by means of ¹H NMR spectroscopy.

One-Step Preparation of Block Copolymer Vesicles with Preferentially Segregated Acidic and Basic Corona Chains**

Laibin Luo and Adi Eisenberg*

Amphiphilic molecules, such as block copolymers,^[1–10] phospholipids,^[11, 12] synthetic surfactants,^[13, 14] and other amphiphiles^[15–18] can self-assemble to form vesicles in aqueous solutions. The equilibrium nature of vesicles has received considerable attention. It has been suggested that vesicles prepared from surfactant mixtures made by combining oppositely charged surfactants are equilibrium structures. The free energy is minimized in vesicles through different concentrations of the two surfactants on each side of the bilayer.^[19–22] Alternatively, small-molecule vesicles can also be stabilized by grafting a polymer to the outer layer.^[23] Very recently, the thermodynamic stabilization mechanism of diblock copolymer vesicles was elucidated by our research group.^[24] In vesicles prepared from polystyrene-*b*-poly(acrylic acid) (PS-*b*-PAA) diblock copolymers, it has been shown that shorter PAA chains are segregated into the inside of the vesicles, while the longer PAA chains are segregated on the outside. The repulsions among the longer PAA chains on the outside are stronger than those among the shorter PAA chains on the inside, thus stabilizing the curvature of the vesicles. Preferential segregation of blocks of different lengths was proved by the use of fluorescently labeled diblock copolymers in which pyrene was located at the junction point between the hydrophilic and hydrophobic blocks. If the vesicles were prepared in a dioxane–water mixture (40 % water content) with a labeled copolymer containing short hydrophilic segments, the pyrene was mostly inaccessible to the quencher because it was located on the inside of the vesicles. By contrast, pyrene molecules attached to the block copolymers with long hydrophilic chains were accessible to the quencher because they were on the outside. It was also shown that segregation is dependent on the size of the vesicles and that it is reversible in response to changes of size.^[25] On the basis of this evidence it was suggested that vesicles are equilibrium structures in dioxane–water mixtures.

Since corona chains can be directed preferentially to either the inside or the outside of the vesicles, it is clear that the technique can, in principle, be utilized to locate chemically distinct groups on the inside or outside of the vesicles. Herein we show this is indeed possible by exploring the segregation of a mixture of polystyrene diblock copolymers containing both polystyrene-*b*-poly(acrylic acid) (PS-*b*-PAA) and polystyrene-*b*-poly(4-vinylpyridine) (PS-*b*-P(4-VP)). Although one of

these blocks is acidic and the other one is basic, we show that they can be preferentially segregated on the inside and outside of the vesicles, respectively, by using different hydrophilic block lengths. One aspect of the proof of segregation consists of the use of a fluorescently labeled diblock of PS₂₉₅-Py-*b*-PAA₁₂ (with a pyrene molecule (Py) located between the styrene and the acrylic acid blocks) mixed with unlabeled PS₃₀₀-*b*-PAA₁₁ as the acidic component. If segregation occurs in this system we expect the pyrene to be largely inaccessible to the quencher. Another element of the proof of segregation consists of a comparison of the ζ potential of vesicles prepared from only PS₃₁₀-*b*-P(4-VP)₃₃ and others of only PS₃₀₀-*b*-PAA₄₄ with that of vesicles prepared from the mixed copolymers.

It is worth noting that asymmetric diblock copolymers in solution can self-assemble into aggregates of a range of morphologies; vesicles are a part of a morphological continuum of crew-cut aggregates which include spheres, rods, vesicles, inverse micellar aggregates, and, in some cases, also bicontinuous and hollow-rod structures.^[2] A balance of the free energy associated with the interfacial energy between the core and the outside solution, the stretching of the core-forming blocks, and the repulsive interactions among the corona chains controls the morphologies of the crew-cut aggregates.^[26] Thus, morphologies can be controlled by many factors, such as relative block length,^[2a,b] ion content,^[2c,d] and solvent composition,^[2f,h] all of which influence one or more of the three free-energy contributions.^[26]

In our studies, five distinct block copolymers and mixtures were considered. Transmission electron microscopy (TEM) was used to investigate the morphologies of the aggregates. As shown in Figure 1a and b, PS₃₀₀-*b*-PAA₁₁ self-assembles into large compound micelles (LCMs); while PS₃₁₀-*b*-P(4-VP)₃₃ self-assembles into vesicles under the conditions described in the experimental section. The vesicles have an average outside diameter ($\pm$ standard deviation) of 102 ± 14 nm and an average wall thickness of 26 ± 2 nm. Only vesicles were observed in the mixture of the two diblock copolymers (Figure 1c). The average diameter and wall thickness are 90 ± 12 nm and 26 ± 2 nm, respectively. The sizes of vesicles prepared from the mixture are somewhat smaller than those prepared from the single component; the wall thickness, however, is the same. The pyrene-labeled diblock copolymer mixture also forms vesicles (Figure 1d). Both the average diameter (88 ± 11 nm) and wall thickness (26 ± 2 nm) are similar to those of vesicles prepared from unlabeled mixture. As reported previously, PS₃₀₀-*b*-PAA₄₄ can self-assemble into vesicles with an average diameter of 98 ± 7 nm and a wall thickness of 26 ± 3 nm in a dioxane–water solvent mixture containing 1 % polymer and 40 % water.^[24]

The outside surface properties of PS₃₁₀-*b*-P(4-VP)₃₃, PS₃₀₀-*b*-PAA₄₄, and PS₃₀₀-*b*-PAA₁₁/PS₃₁₀-*b*-P(4-VP)₃₃ vesicles were investigated by measurement of the ζ potential.^[27] Figure 2 shows the plots of the ζ potential versus pH for vesicles prepared from these three different systems. The outside corona of the PS₃₁₀-*b*-P(4-VP)₃₃ vesicles consists of only P(4-VP) chains. The 4-VP units are protonated at pH 3 and, therefore, the PS₃₁₀-*b*-P(4-VP)₃₃ vesicles show a positive ζ potential. The degree of protonation of P(4-VP) decreases with increasing pH, and hence the ζ potential decreases.^[28]

[*] Prof. Dr. A. Eisenberg, Dr. L. Luo
Department of Chemistry
McGill University, 801 Sherbrooke Street West
Montreal, PQ H3A 2K6 (Canada)
Fax: (+1) 514-398-3797
E-mail: adi.eisenberg@mcgill.ca

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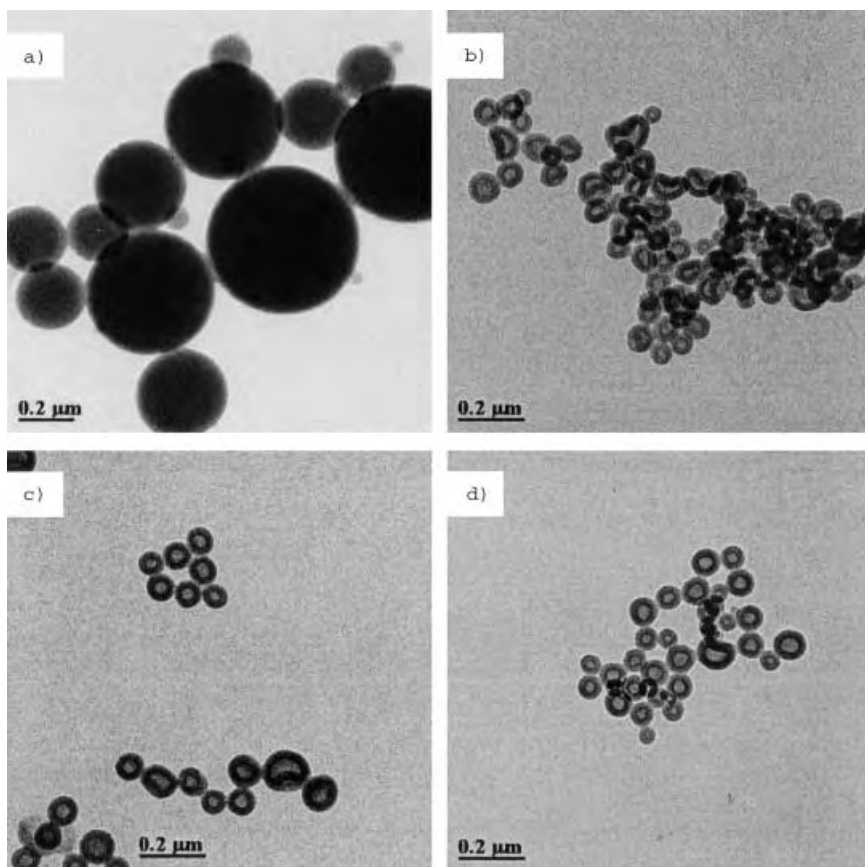


Figure 1. Transmission electron micrograph of aggregates prepared from DMF solution (pH 3.0) of a) $\text{PS}_{300}\text{-}b\text{-PAA}_{11}$ (polymer weight: 0.49 %); b) $\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ (polymer weight: 0.81 %); c) $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ (polymer weight: 0.49/0.81 %; molar ratio: 2/3); d) $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{295}\text{-Py-}b\text{-PAA}_{12}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ (polymer weight: 0.43/0.06/0.81 %; molar ratio: 7/1/12) by adding water to 50 %.

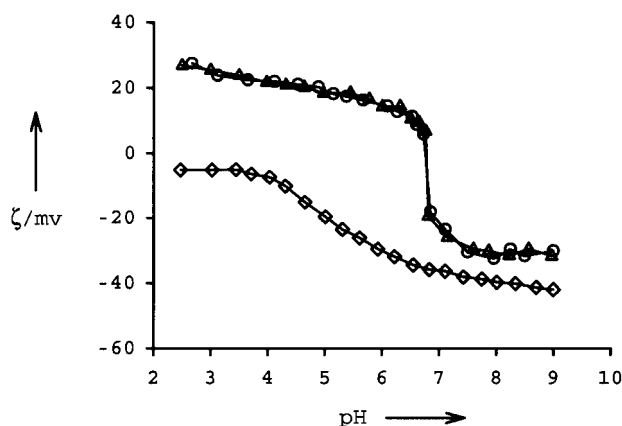


Figure 2. Plots of ζ potential versus pH of vesicles of $\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ (Δ), $\text{PS}_{300}\text{-}b\text{-PAA}_{44}$ ($\diamond$), and $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ (molar ratio: 2/3, $\circ$).

The zeta ζ potential becomes negative in the pH region above 6.8. As reported previously, the pK_a value of P(4-VP) at zero protonation is 5.0.^[29] Thus, the H^+ ions can not play a role in determining the value of the ζ potential in the region above pH 6.8. The reason that the ζ potential becomes negative above pH 6.8 is, most likely, because of the adsorption of anions, that is, OH^- , as was suggested by several research

groups.^[30] In contrast to the vesicles prepared from $\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$, the outside corona of the $\text{PS}_{300}\text{-}b\text{-PAA}_{44}$ vesicles consists only of PAA chains. The degree of ionization of PAA increases with increasing pH value.^[31] Hence, the ζ potential of the $\text{PS}_{300}\text{-}b\text{-PAA}_{44}$ vesicles is negative and decreases further with increasing pH value (Figure 2). The changes in the ζ potential with pH for mixed vesicles of $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ in aqueous solution are also given in Figure 2. The plot is identical to that for $\text{PS}_{310}\text{-}b\text{-P(4VP)}_{33}$ vesicles. This result suggests that the outside corona of $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ vesicles consists mainly of P(4-VP) chains.

It should be noted that poly(vinylpyridine) is not stable in aqueous solution above pH 5.0. Nevertheless, it is possible to determine the pH dependence of the ζ potential above pH 5.0 using our instrumentation (see below), because the vesicles precipitate very slowly. The speed of precipitation was studied semi-quantitatively by monitoring the turbidity as a function of time for both $\text{PS}_{310}\text{-}b\text{-P(4VP)}_{33}$ vesicles as well as those prepared from the mixture of $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ after changing the pH value of the solutions from 3.0 to 7.0 (Figure 3). The decrease in the turbidity results from the settlement of vesicles under the force of gravity. The slow rate of settling shows

that over the time scale used for measuring the ζ potential (less than 10 seconds for the measurement of the ζ potential itself and less than 5 minutes for the preparation of the solution). The turbidity is essentially constant. More importantly, the results obtained for the settlement rates at pH 7.0 (Figure 3) confirm that the extended surfaces of the vesicles prepared from $\text{PS}_{310}\text{-}b\text{-P(4VP)}_{33}$ and the mixture of $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$

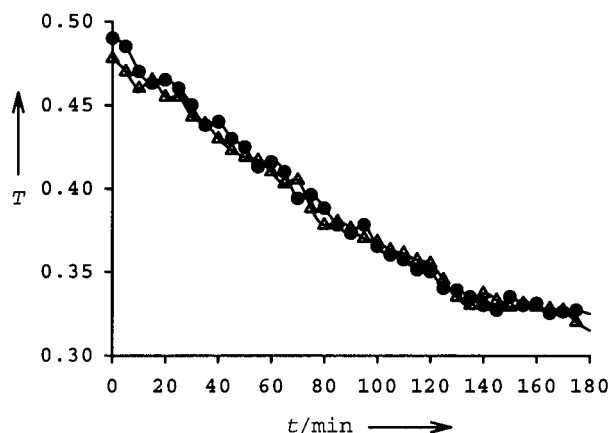


Figure 3. Change of turbidity T versus time for solutions of $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ (Δ) and $\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ ($\bullet$) vesicles (pH 7.0, 7.5 mM NaCl, 0.05 % polymer concentration).

$b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ have the same properties. The slowness of the precipitation process in the micelles, relative to what is observed in the homopolymer, is probably a result of the presence of the hydrophobic surface in the vesicles which can adsorb ions and thus extend considerably the length of time the vesicles remain in solution at $\text{pH} > 5.0$.

The location of the PAA chains was explored using a mixture of block copolymers consisting of $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{295}\text{-Py-}b\text{-PAA}_{12}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ (molar ratio: 7/1/12). The location of the pyrene molecules in the vesicles can be determined by fluorescence quenching experiments using Ti^+ ions as a quencher. Once the vesicles were prepared, they were quenched in water and dialyzed against water. Subsequently, various amounts of Ti^+ ions were added to the solutions of the vesicles and the fluorescence was measured. If pyrene molecules were located on the outside of the vesicles they would be exposed to the Ti^+ ions, and would thus experience efficient quenching. By contrast, the pyrene molecules located on the inside surface are not accessible to Ti^+ ions, and their fluorescence would not be quenched.^[24] The results of the steady-state quenching experiments are shown in Figure 4, plotted as I_0/I versus the quencher

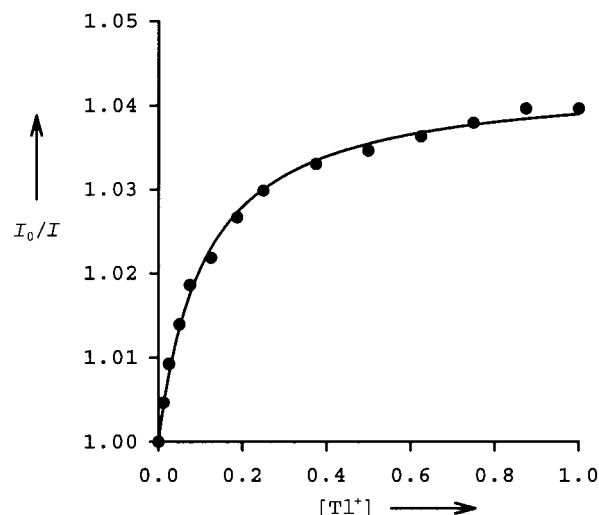


Figure 4. Steady-state fluorescence quenching by Ti^+ ions for $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{295}\text{-Py-}b\text{-PAA}_{12}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ (molar ratio: 7/1/12) vesicles.

concentration. I_0 is the fluorescence intensity without quencher, while I is the steady-state fluorescence in the presence of quencher. The modified Stern–Volmer equation [Eq. (1)] was used to fit the data.^[24, 25, 32]

$$\frac{I_0}{I} = 1 + \frac{\phi K [\text{Ti}^+]}{1 + (1 - \phi) K [\text{Ti}^+]} \quad (1)$$

K is the Stern–Volmer constant and ϕ is the fraction of accessible chromophores. The best-fit ϕ and K values are 0.042 ± 0.001 and $9.5 \pm 0.5 \text{ mM}^{-1}$, respectively; the line was, in turn, calculated from these numbers. The results suggest that 4.2% of the pyrene molecules are accessible to the Ti^+ ions in the solution, which means that approximately 96% of the molecules are inaccessible because they are located on the inside of the vesicles. Therefore, it can be concluded that the

PAA chains are mainly segregated on the inside of the $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{295}\text{-Py-}b\text{-PAA}_{12}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ vesicles.

In conclusion, we have shown that polymeric vesicles can be prepared from a diblock copolymer mixture of $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$. The PAA block chains in $\text{PS}_{300}\text{-}b\text{-PAA}_{11}$ are segregated into the inside of the vesicles, while the outside corona of the vesicles consist of P(4-VP) chains. This segregation occurs because the PAA chains are much shorter than the P(4-VP) chains and stabilize the curvature. Another factor which contributes to the curvature stabilization is that the P(4-VP) chains are positively charged (which implies a repulsive interaction in solution), while PAA chains are neutral under the experimental conditions. The one-step assembly of vesicles in which one species is attached to the inside wall and another to the outside, as demonstrated here, may have useful applications.

Experimental Section

Micellization: A mixture of $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ was dissolved in DMF (polymer weight: 0.49/0.81 %, w/w; molar ratio: 2/3). The pH value was adjusted to 3 using 4 M HCl to protonate the vinylpyridine units in order to avoid formation of complexes between PAA and P(4-VP). To induce micellization, water was added at a rate of 0.1 % per minute to the solution until a water content of 50 % was reached. The colloid solution was then quenched by excess water and dialyzed against water. As controls, the micellization of $\text{PS}_{300}\text{-}b\text{-PAA}_{11}$ and $\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ was also performed under the same conditions and following the same procedure. Furthermore, a diblock copolymer mixture of $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{295}\text{-Py-}b\text{-PAA}_{12}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ (polymer weight %: 0.43/0.06/0.81, w/w/w; molar ratio: 7/1/12) was used to prepare fluorescently labeled aggregates.

Transmission electron microscopy was performed on a JEOL microscope with a CCD camera operating at an acceleration voltage of 80 kV. Copper EM grids were precoated with a thin film of Formvar and then coated with carbon. A drop of solution containing 0.05 wt % of polymer was deposited on the resulting grids. Samples were dried in air overnight.

The mobility of the vesicles was determined in aqueous 7.5 mM NaCl solutions at 25 °C over a pH range of 3–9 on a MKII Microelectrophoresis Instrument to obtain the ζ potential of the samples. The pH value of the solutions was altered by adding 7.5 mM HCl or NaOH solutions.

For the turbidity measurements, the $\text{PS}_{300}\text{-}b\text{-PAA}_{11}/\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ and $\text{PS}_{310}\text{-}b\text{-P(4-VP)}_{33}$ vesicles were dispersed at pH 3.0 in a 7.5 mM NaCl solution. The pH value was adjusted to pH 7.0 by adding a 7.5 mM NaOH solution. The turbidity of solutions was monitored at a wavelength of 650 nm.

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A Method To Identify and Screen Libraries of Guests That Complex to a Synthetic Host**

Menno R. de Jong, Ronald M. A. Knegtel,
Peter D. J. Grootenhuys, Jurriaan Huskens,* and
David N. Reinhoudt*

In supramolecular host–guest chemistry, the de novo design of a host molecule often does not lead to selectivity for the desired guest.^[1] Alternatively, host–guest recognition can be reformulated from the perspective of a known host molecule that requires the identification of suitable guest molecules. This would allow the application of existing host molecules in other fields, for example, for sensing other guest molecules, or for carrying other drugs in artificial drug-carrier systems. The identification of guests is a well-known problem in medicinal chemistry, where lead discovery aims at the identification of possible binders to an enzyme, for example. In this field, one approach to overcome the limitations of de novo design is the development of rapid (virtual) screening techniques.

Docking is a computational method often used to identify new leads or suggest possible binding modes of known guests.^[2] When used for the identification of leads, docking starts from a simplified representation of the binding pocket of a protein or receptor, for example, one derived from a crystal structure. Subsequently, a large number of potential ligands are fitted into this binding site and the docking algorithm finds guests that yield a favorable interaction energy with the host. The success of this approach in identifying potential binders for a receptor inspired us to investigate whether it would also allow the rapid screening of large numbers of guests for synthetic receptors.

In supramolecular chemistry, cyclodextrins (Figure 1a) are often used because of their unique ability to complex a variety of small organic guests in water.^[3] Previously, we reported the binding properties of cyclodextrin dimer **1** (Figure 1b) with cholates and the fluorescence-signaling behavior of a closely related dansyl-appended dimer.^[4] Recently, a number of cyclodextrin dimers have been reported and these often exhibit enhanced binding with suitable guests,^[5] some of them as stable as enzyme–ligand interactions. This renders these

[*] Dr. Ir. J. Huskens, Prof. Dr. Ir. D. N. Reinhoudt, Dr. M. R. de Jong, Prof. Dr. P. D. J. Grootenhuys
Laboratory of Supramolecular Chemistry and Technology
MESA⁺ Research Institute, University of Twente
PO Box 217, 7500 AE Enschede (Netherlands)
Fax: (+31) 53-489-4645
E-mail: SMCT@ct.utwente.nl
Dr. R. M. A. Knegtel
Vertex Pharmaceuticals (Europe) Ltd.
88 Milton Park, Abingdon, Oxfordshire OX14 4RY
(United Kingdom)

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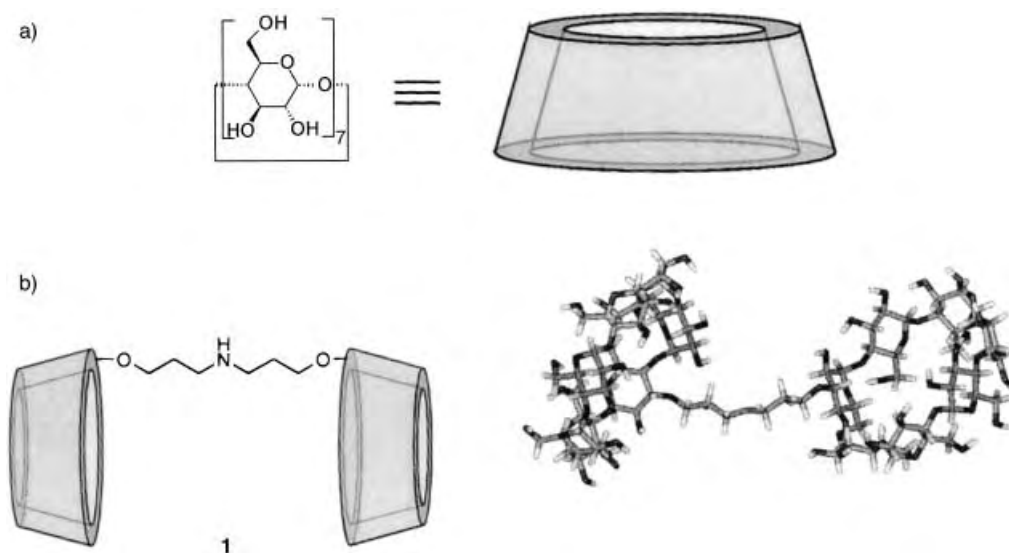


Figure 1. a) Structure of β -cyclodextrin; b) schematic representation (left) and energy-minimized structure (right) of cyclodextrin dimer **1**.

cyclodextrin derivatives interesting candidates for comparing the computational and experimental assessment of binding properties. Computational methods have been used to identify binding modes for known guests into cyclodextrins.^[6] In the present study we have performed a docking procedure with one synthetic host and many guest molecules, and have subsequently tested its success score by experimental verification of the complexation strength by using a facile and rapid fluorescence assay.

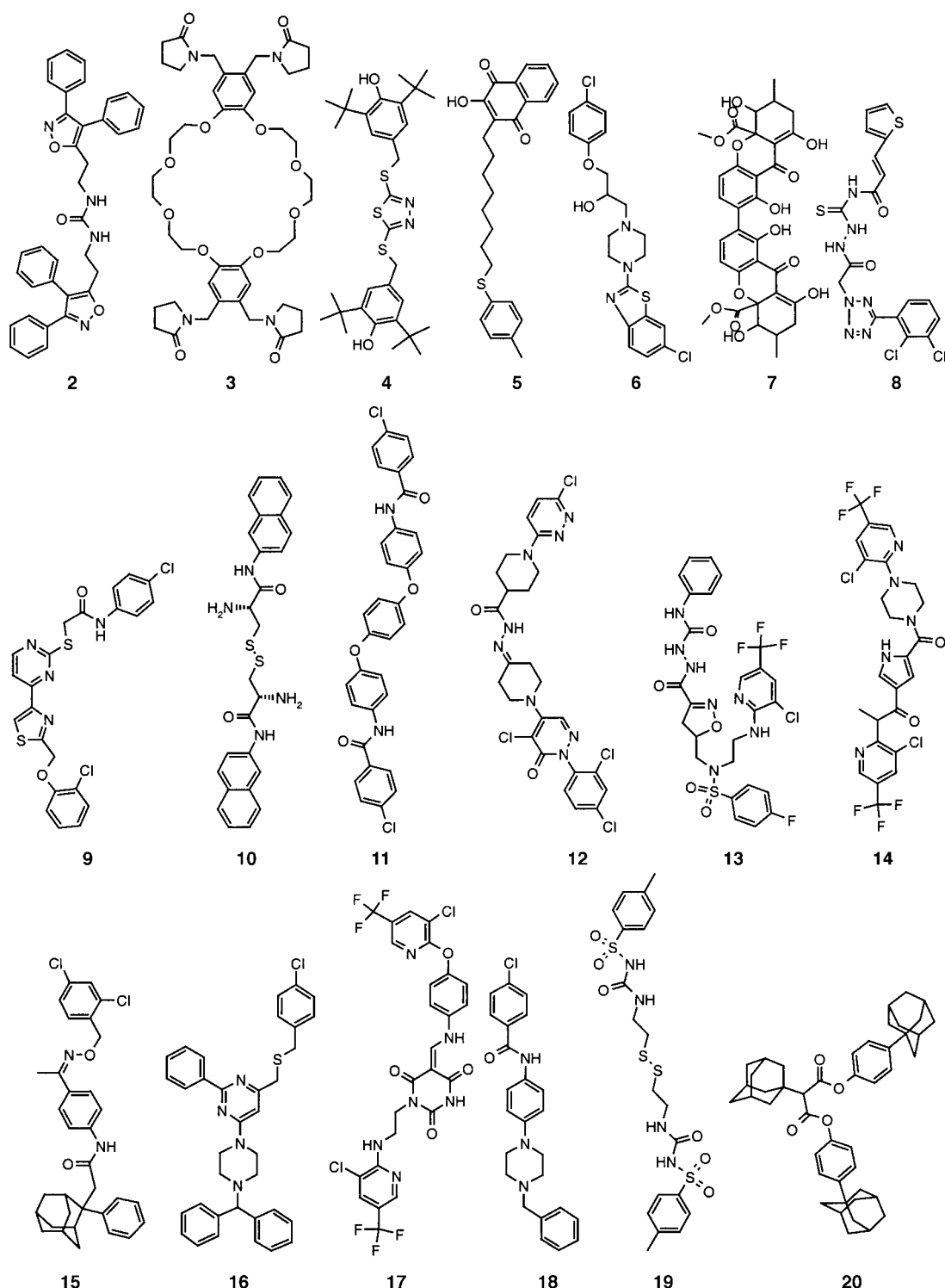
As there is no crystal structure of the cyclodextrin dimer (**1**), its conformation used in the docking procedure was generated by a molecular mechanics study of **1** based on a crystal structure of native β -cyclodextrin and an extended conformation of the flexible alkyl spacer (Figure 1b).^[7] This conformation was used for docking with the Available Chemicals Database (ACD) and the Comprehensive Medicinal Chemistry Database (CMCD). Ligands with molecular weights below 200 D and compounds with more than two formal charges or reactive functionalities were excluded, and the remaining $\sim 10^5$ molecules from the ACD and $\sim 10^4$ molecules from the CMCD were docked in **1**. The highest ranking structures, about 500 from the ACD and 200 from the CMCD, were visually inspected. Among the highest ranking docking solutions for molecules from the ACD, several are of sufficient length to position hydrophobic functionalities in both β -cyclodextrin cavities. In particular, phenyl, cyclohexyl, adamantyl, *tert*-butyl, and complex aliphatic ring systems (steroid- or opiate-like) were found to be located in the β -cyclodextrin ring interiors. In some cases, additional hydrogen bonding to hydroxy groups of the cyclodextrin rings was also suggested. The interaction with the linker moiety was usually minimal.

For the majority of ligands retrieved from the CMCD, binding to both cyclodextrins appeared to be less common. This is to be expected since the CMCD contains drug molecules that typically have relatively low molecular weights (< 600) and corresponding small molecular sizes. Although traditionally applied in virtual screening of protein guests,^[2]

molecular database docking appears to perform well as a computational tool to identify small molecule guests for synthetic receptors. After visual inspection of docking hits, a total of 93 ligands from the ACD and 125 ligands from the CMCD were selected for experimental evaluation (subject to commercial availability). A selection of these hits had to be made since the experimental evaluation not only required commercial availability, but also high purity of the compound and solubility in water (or at least in methanol). Many compounds from the CMCD are not commercially available in pure form. Thus, this number was reduced to 30 guests: 19 from the ACD (Scheme 1), and 11 from the CMCD (Scheme 2).^[8]

For a rapid indication as to whether a guest binds or not, we performed a fluorescence competition assay in which the guests to be screened compete for binding to **1** with a fluorophore of known binding strength. We employed the polarity probe 2-*p*-toluidinylnaphthalene-6-sulfonate (TNS), the fluorescence intensity of which increases strongly upon binding to cyclodextrin or cyclodextrin dimers.^[5e, 9] Its binding constant to **1** ($5.3 \times 10^4 \text{ M}^{-1}$) was determined by means of a fluorescence titration. The binding constants of most known guests in native β -cyclodextrin are in the range of $10^2 - 10^4 \text{ M}^{-1}$; only a few stronger binding guests are known. Therefore, a threshold value of 10^5 M^{-1} for the association constant was taken as an indication that both cavities cooperate in guest binding. The screening was performed by the addition of a concentrated methanolic solution of the competing guest to an aqueous solution of **1** and TNS.^[10] The results are summarized in Figure 2.

We found that three guests from the ACD (**5**, **8**, and **13**) and six from the CMCD (**21–26**) bind strongly to dimer **1**, since competition fluorescence titrations revealed association constants $> 10^5 \text{ M}^{-1}$.^[11] Given the absence of terms that account for entropic effects from the force field score applied in this study and the use of rigid molecular structures, little correlation is expected between predicted binding enthalpies and measured binding constants. The correlation between predicted and



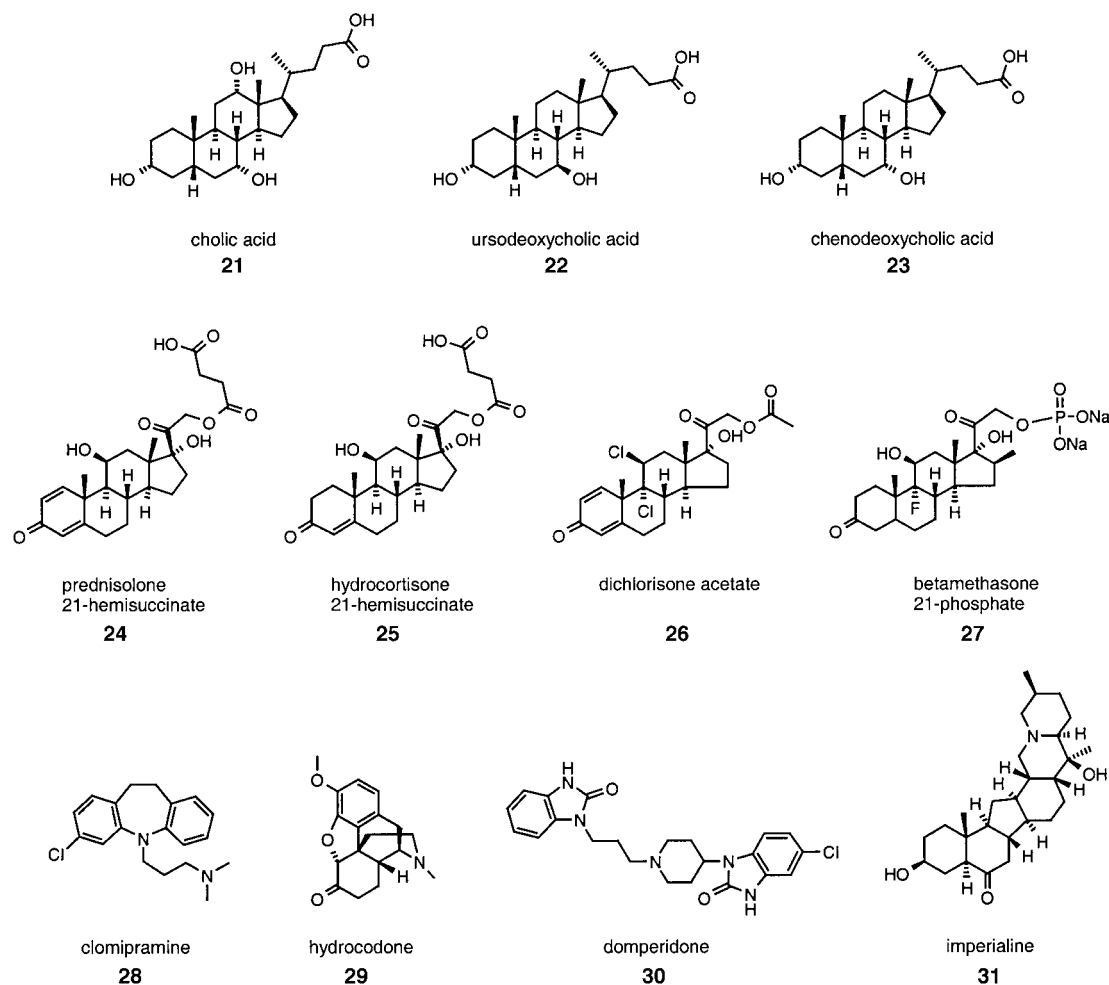
Scheme 1. Compounds from the Available Chemicals Database (ACD) selected for screening.

measured binding constants also remains a problem for molecular docking applications in medicinal chemistry.^[12] In principle, however, this does not prohibit virtual screening from identifying suitable ligands for receptors.

The hit rate of 9 out of 30 (30%) compares very favorably to the results obtained with docking of ligands to bioreceptors, for which hit rates are usually <10%. The favorable hit rate obtained when using a cyclodextrin receptor with respect to

similar applications in medicinal chemistry can be explained from the relative structural simplicity of the synthetic receptor.^[13] A summary of the various stages that led to the identification of the nine strongly bound guests is shown in Figure 3.

Molecular docking to synthetic receptors is probably subject to similar sources of error as virtual screening of molecule databases with biological receptors.^[14] The scoring



Scheme 2. Compounds from the Comprehensive Medicinal Chemistry Database (CMCD) selected for screening.

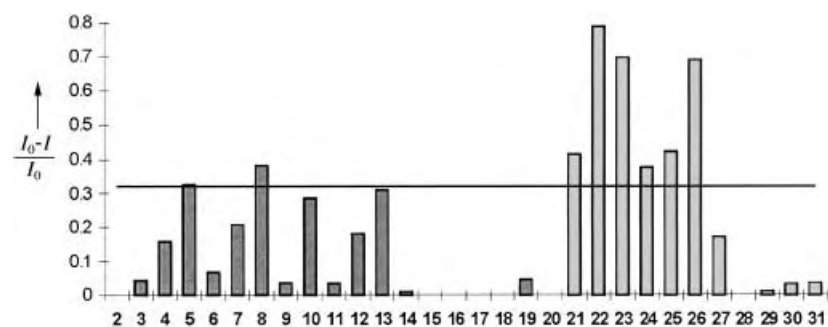


Figure 2. Overview of the screening of guests found by the docking procedure. The solid line represents the calculated response for a K value of the competing guest of 10^5 M^{-1} .

protocol, which involves rigid ligand conformations and force-field scoring without correction for entropic effects, is able to identify novel ligands for cyclodextrin-derived receptors with such an impressive degree of accuracy.

This work demonstrates the potential for virtual screening methodologies outside the confines of pharmaceutical lead identification. In future, similar computational procedures as the one described here may also provide a useful tool in the design of synthetic receptors for a given guest.

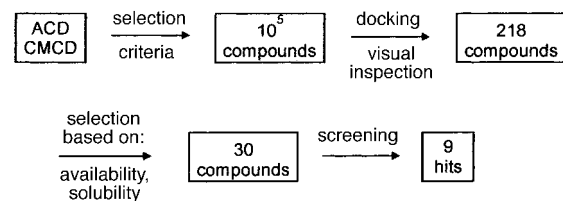


Figure 3. Stages of the docking procedure.

function, the computational implementation, and the degree of conformational sampling of ligands and receptor influence the results. However, it is encouraging that a relatively simple

Experimental Section

Computational methodology: To identify small organic molecules that bind both cyclodextrin cavities of the dimer, the molecular docking program DOCK 4.0^[15] was applied. Two chemical databases supplied by MDL Information Systems Inc. (San Leandro, USA) were considered for docking. The Available Chemicals Database (ACD, version 2000.1) provides a source of commercially available small organic molecules, while the Comprehensive Medicinal Chemistry Database (CMCD, version 98.1) is a source of currently marketed drugs and other molecules of medical importance. Three-dimensional structures for potential ligands from the ACD and CMCD were generated by using the CORINA program^[16] (version 1.81). The linear shape of the dual cyclodextrin receptor molecule

suggests preferred binding of molecules in an extended conformation. It was therefore decided to use directly the extended ligand conformations commonly generated by the CORINA program without allowing for additional ligand flexibility during docking. After filtering out ligands with molecular weights below 200, more than two formal charges, and reactive functionalities, a total of 70867 molecules from the ACD and 7497 molecules from the CMCD were docked against the β -cyclodextrin dimer.

Docking of rigid ligand molecules involves their superposition onto site points in the receptor molecule. Docking site points, covering the binding pockets of both cyclodextrin host molecules, were generated with SPHGEN^[17] and limited to a total of 25 by means of visual inspection with Quanta 98 (Molecular Simulations Inc., San Diego, USA). The highest ranking molecules were visually inspected by using Quanta98 and web tools that apply the Chime plug-in (MDL, San Leandro USA). For the ACD, three sets of the 500 best scoring molecules with total charges of 0, 1, and 2 were visually inspected. For the smaller CMCD, the total number of molecules visually inspected was 200. Since the force-field-based scoring function used by DOCK 4.0 does not take entropic contributions to host–guest binding into account (i.e. solvation, flexibility) further manual filtering was applied to the docked solutions. Visual inspection implied removal of docking solutions that placed charged or polar functionality in the hydrophobic interior of the cyclodextrin ring or exposed large hydrophobic groups to the solvent. Furthermore, duplicates (i.e. different salts of the same compound) were removed and molecules that bind to both cyclodextrin units of the dimer were preferred over smaller molecules. Those ligands that display good complementarity to the cyclodextrin dimer were selected for testing. More information on the calculations is given in the Supporting Information.

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- [11] Fluorescence competition titrations were performed by adding aliquots of a solution of the guest ($6.1 \times 10^{-4} \text{ M}$) in methanol to an aqueous solution (3 mL) of **1** ($2.0 \times 10^{-6} \text{ M}$) and TNS ($1.0 \times 10^{-5} \text{ M}$) finally reaching a maximum of 3% v/v of methanol. After each addition, the fluorescence spectrum was recorded. The binding constants for **21**, **22**, and **23** have been reported before.^[4] The others are: **5**: $1.0 \times 10^5 \text{ M}^{-1}$; **8**: $1.9 \times 10^5 \text{ M}^{-1}$; **13**: $1.6 \times 10^6 \text{ M}^{-1}$; **24**: $3.4 \times 10^5 \text{ M}^{-1}$; **25**: $4.3 \times 10^5 \text{ M}^{-1}$; **26**: $3.6 \times 10^6 \text{ M}^{-1}$.
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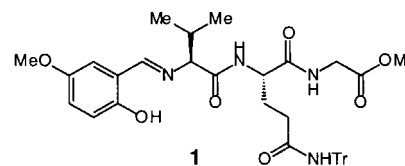
Aluminum-Catalyzed Asymmetric Addition of TMSCN to Aromatic and Aliphatic Ketones Promoted by an Easily Accessible and Recyclable Peptide Ligand**

Hongbo Deng, Markus P. Isler, Marc L. Snapper,* and Amir H. Hoveyda*

We have recently developed a number of catalytic asymmetric C–C bond-forming reactions that are promoted by chiral peptidic ligands in the presence of early or late transition metals.^[1] Among these transformations are the Ti-catalyzed enantioselective additions of cyanide to epoxides^[2] and imines.^[3] Subsequent to the above studies, we set out to develop another important C–C bond-forming process: catalytic asymmetric synthesis of tertiary cyanohydrins by the addition of cyanide to a wide range of ketones, electrophiles for which only a few examples of catalytic asymmetric reactions involving carbon nucleophiles exist.^[4] Such transformations would be of notable synthetic utility, since the resulting cyanohydrins can be converted into numerous optically pure or enriched synthons (e.g., tertiary α -hydroxy carbonyl compounds).^[5]

Belokon has reported a Ti-catalyzed addition of TMSCN (TMS = trimethylsilyl) to aromatic ketones, in which a C_2 -symmetric Schiff base is employed as the chiral ligand.^[6] Shibasaki has disclosed enantioselective catalytic additions of TMSCN to aromatic and aliphatic ketones.^[7] In the latter studies, a carbohydrate-derived bifunctional ligand and $Ti(OiPr)_4$ promote the asymmetric additions. Most recently, Deng and Tian have outlined a method for cyanide addition to ketones with cyanoformate and catalytic amounts of cinchona alkaloids.^[8] In spite of these important advances,^[9–10] several pressing problems remain unresolved. Among these are the relatively low levels of enantioselectivity obtained with acyclic aliphatic ketones, especially in cases where there is little steric difference between the two substituents, and the long routes required for the synthesis of some of the more effective chiral ligands (up to thirteen linear steps).

Herein, we report a new approach to asymmetric cyanation of ketones that is Al-catalyzed, utilizes a peptidic chiral ligand, and delivers high enantioselectivity with both aromatic and aliphatic ketones. In addition, this method provides several practical advantages: it requires a recyclable chiral ligand **1** that is readily modifiable and can be easily synthesized in six simple steps and in 75% overall yield. In several cases, the method delivers higher levels of asymmetric



induction than reported previously (particularly with aliphatic ketones).

To identify an effective chiral ligand and metal salt for the catalytic addition, we carried out systematic screening studies, taking advantage of the modularity of peptide-based chiral ligands and following protocols developed in our laboratories.^[11] Acetophenone (**2**) was used as the substrate and TMSCN was selected as the nucleophile.^[12] We were therefore able to establish that chiral peptide ligand **1** and $Al(OiPr)_3$ effectively promote the enantioselective addition of TMSCN to **2**. These studies included an examination of various additives,^[13] leading us to determine that the combined presence of MeOH and 3-Å molecular sieves are critical to reactivity as well as selectivity levels (see below for details).^[12] Thus we find that treatment of acetophenone (**2**) with TMSCN in the presence of dipeptide Schiff base **1** (20 mol %), $Al(OiPr)_3$ (20 mol %), MeOH (20 mol %), and 3-Å molecular sieves (2 equiv) leads to the efficient (>98% conversion) formation of cyanohydrin **3** in 88% *ee* and 93% yield (Table 1, entry 1).

The data illustrated in Table 1 demonstrate that a variety of aromatic ketones may be employed in the Al-catalyzed process. Reaction efficiencies and asymmetric inductions are not adversely influenced by electron-rich (Table 1, entry 3) or electron-deficient aryl substituents (Table 1, entries 4–7). Sterically hindered ketone **10** undergoes reaction to afford **11** efficiently (83% yield) and in 94% *ee*. Al-catalyzed asymmetric syntheses of **13** and **15** illustrate that this method is effective with cyclic substrates other than methyl aryl ketones (Table 1, entries 8, 9). Catalytic additions to **16** and **18** (Table 1, entries 10, 11) demonstrate that cyclic ketones are suitable substrates.

It is important to mention that ligand **1** can be easily recovered and used in subsequent asymmetric cyanide additions. As an example, **1** is recovered by silica-gel chromatography in >98% yield from the conversion of **2** into **3**. Subsequent use of the recovered ligand delivers similar levels of reactivity and selectivity. It must also be noted that either 10 or 20 mol % catalyst may be used. Although longer reaction times are required with reduced catalyst loading (10 mol % **1**, 72 h), the desired product is isolated without loss of enantioselectivity (Table 1, entries 2 and 5).

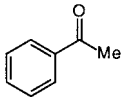
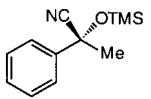
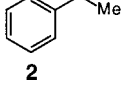
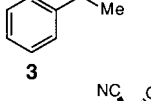
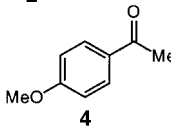
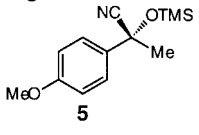
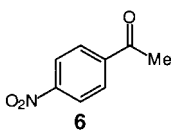
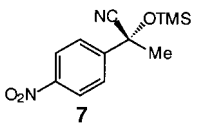
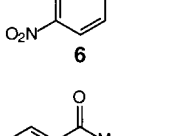
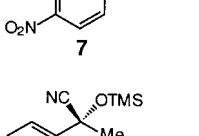
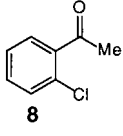
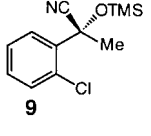
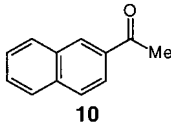
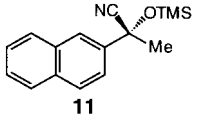
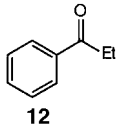
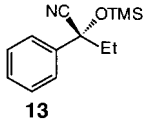
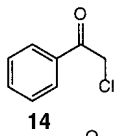
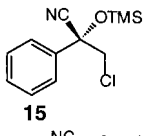
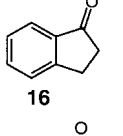
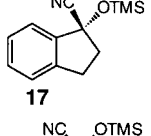
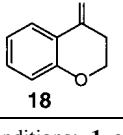
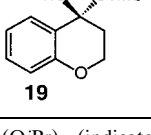
Acyclic aliphatic ketones can also be used in these Al-catalyzed additions; the corresponding cyanohydrins are isolated in >65% yield with high enantioselectivity. Both saturated (Table 2, entries 1, 2, and 4) and α,β -unsaturated alkenyl and alkynyl ketones (Table 2, entries 3 and 5–8) serve well as substrates. The unsaturated acyclic ketones, in particular, afford products of higher enantiopurity. Reactions may be effected in the presence of 10 mol % **1** and $Al(OiPr)_3$ without diminution in enantioselectivity or yield (Table 2, entries 2, 6, and 8). The highly enantioselective addition to **28**

[*] Prof. M. L. Snapper, Prof. A. H. Hoveyda, Dr. H. Deng, Dr. M. P. Isler
Department of Chemistry, Merkert Chemistry Center
Boston College
Chestnut Hill, MA 02467 (USA)
Fax: (+1) 617-552-1442
E-mail: amir.hoveyda@bc.edu

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Table 1. Al-catalyzed enantioselective addition of TMSCN to aromatic ketones.^[a]

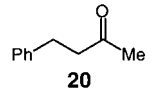
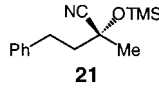
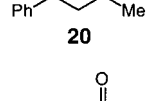
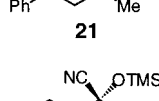
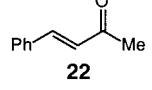
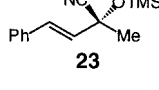
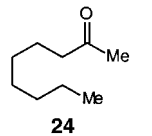
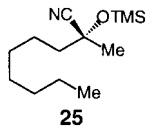
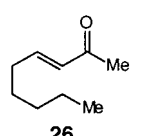
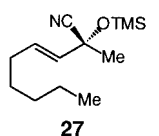
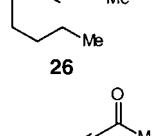
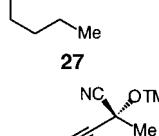
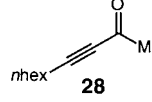
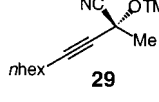
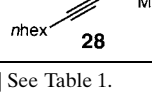
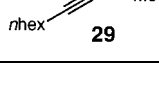
Entry	Substrate	Product	mol % 1 and Al(OiPr) ₃	Yield [%] ^[b]	ee [%] ^[c]
2			10	84	91
1			20	93	88
3			20	67	91
4			20	> 98	88
5			10	92	90
6			20	87	85
7			20	83	94
8			20	98	88
9			20	87	80
10			20	87	88
11			20	85	88

[a] Conditions: **1** and Al(OiPr)₃ (indicated amounts), MeOH (20 mol %), TMSCN (2 equiv), molecular sieves (3 Å, 2 equiv by weight relative to substrate), toluene, -78 °C, 48 h (72 h for entries 2 and 5). [b] Conversions determined by GLC analysis (>98% in all cases). Yields after silica-gel chromatography. [c] All enantioselectivities determined by chiral GLC (CDGTA column); selectivity in entry 7 determined by chiral HPLC (Chiralpak OJ column).

(Table 2, entries 7, 8) to afford cyanohydrin **29** is noteworthy (91% ee), as it illustrates that the present Al-catalyzed protocol may deliver high levels of enantioselectivity even when there is a modest steric difference between the two carbonyl substituents.

The particulars of the mechanism of the Al-catalyzed process must await the outcome of detailed kinetic and

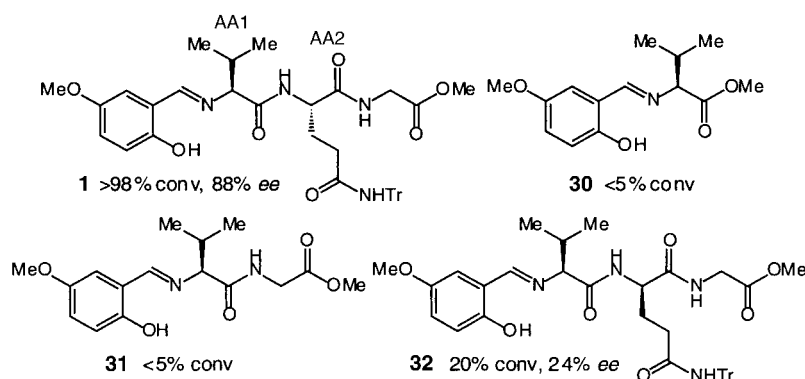
Table 2. Al-catalyzed enantioselective addition of TMSCN to aliphatic ketones.^[a]

Entry	Substrate	Product	mol % 1 and Al salt	Yield [%] ^[b]	ee [%] ^[c]
1			20	93	80
2			10	97	82
3			20	67	95
4			20	93	86
5			20	98	95
6			10	77	95
7			20	78	90
8			10	66	91

[a] – [c] See Table 1.

spectroscopic studies. Nevertheless, the following initial observations shed light on a few aspects of the asymmetric reaction:

- 1) The process is ligand accelerated;^[14] <5% conversion is observed under identical conditions but in the absence of ligand **1**.
- 2) As illustrated in Scheme 1, the presence and the stereochemical identity of the AA2 moiety is pivotal to reaction efficiency and enantioselectivity. These findings suggest cooperative involvement of AA2 in delivering TMSCN or HCN to the Al-bound ketone. Such a scenario would be in agreement with the hypothesis put forth recently, based on extensive kinetic and other physical data, for the Ti-catalyzed cyanide additions to imines.^[15]
- 3) In the absence of additives, reactions are significantly less efficient. For example, conversion of **2** into **3** proceeds to 30–60% conversion (vs >98%) when one or both additives are omitted from the reaction mixture.
- 4) When TMSCN addition to **2** is carried out in the presence of 20 mol % HCN (instead of MeOH), reaction proceeds to 71% conversion and **3** is formed in 81% ee (vs 64% conversion and 86% ee in the absence of HCN or MeOH). Thus, the positive effect of MeOH is likely not due to in situ HCN generation.^[16]
- 5) When [D₃]-**2** (trideuteroacetophenone) is used, little or no variation in reaction efficiency or selectivity is observed. The effect of added MeOH is therefore not linked to regeneration of the ketone substrate by reaction with unreactive metal enolates that may be formed under the reaction conditions. Otherwise, due to the expected slower rate of enolate formation (primary isotope effect), the deuterated analogue would have reacted more readily and/or with higher levels of asymmetric induction.^[4c]



Scheme 1. Reactivity and enantioselectivity as a function of ligand structure; the presence and the relative stereochemistry (relative to AA1) of AA2 is critical to yield and *ee*. Data shown are for additions to ketone **2** under conditions indicated in Table 1 (20 mol % catalyst).

In summary, we have developed a new, efficient, and enantioselective method for the addition of TMSCN to aromatic (cyclic and acyclic) and aliphatic ketones (saturated and unsaturated). Substrates^[17] and chiral ligands are prepared rapidly and efficiently (routine peptide coupling and Schiff base synthesis on a solid phase or in solution) and can be easily modified.^[12] The levels of enantioselectivity observed are either competitive or higher than those reported previously (e.g., **19**, **25**, **29**). Asymmetric synthesis of **29** (Table 2, entries 7, 8) represents the first example of catalytic enantioselective cyanide addition to an alkynyl ketone. This Al-catalyzed C–C bond-forming method should thus prove to be a useful addition to the existing methods for the synthesis of nonracemic quaternary carbon centers.^[18]

Experimental Section

3: Acetophenone (22.8 mg, 150.0 μ mol), peptide Schiff base **1** (20.8 mg, 30.0 μ mol), and powdered molecular sieves (3 Å, 40.0 mg) were suspended in toluene (300.0 μ L). Aluminum isopropoxide (30.0 μ L, 1.0 M in toluene, 30.0 μ mol) and methanol (60.0 μ L, 0.5 M in toluene, 30.0 μ mol) were added successively. The mixture was allowed to stir for 5 min at 22 °C and then cooled to –78 °C. Trimethylsilyl cyanide (150.0 μ L, 2.0 M in toluene, 300.0 μ mol) was added dropwise into the reaction mixture and the resulting mixture was allowed to stir for 48 h at –78 °C. Pentane was added (500.0 μ L) to quench the reaction and the resulting cold slurry was directly purified by silica-gel chromatography (pentane (10.0 mL) to remove toluene, followed by 100:1 pentane/Et₂O). The desired tertiary cyanohydrin **3** was collected as a clear, colorless oil (30.6 mg, 93 %). IR (neat): $\tilde{\nu}$ = 3062 (w), 3024 (w), 2993 (w), 2967 (m), 2904 (w), 1495 (w), 1451 (m), 1369 (w), 1256 (s), 1230 (s), 1155 (s), 1123 (s), 1073 (m), 991 (s), 847 (s), 752 (s), 702 (s) cm^{–1}; ¹H NMR (400 MHz): δ = 7.56–7.53 (m, 2H), 7.41–7.34 (m, 3H), 1.85 (s, 3H), 0.17 (s, 9H); ¹³C NMR (100 MHz): δ = 142.2, 128.9, 124.8, 121.9, 71.8, 33.8, 1.3; HR-MS: calcd for C₁₂H₁₇NOSi: 219.1079; found: 219.1082; elemental analysis: calcd for C₁₂H₁₇NOSi: C 65.71, H 7.81, N 6.39; found: C 65.78, H 7.84, N 6.59; $[\alpha]_D^{20}$ = +18.5° (*c* = 1.25, CHCl₃, 88 % *ee*); GLC (CDGTA: column temperature = 80 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): *t*_r (major) = 46.2 min, *t*_r (minor) = 51.1 min. Absolute configuration was established to be *R* by comparison with optical rotation reported previously [lit. $[\alpha]_D^{20}$ = +21.9 (*c* = 1.18, CHCl₃, 93 % *ee*).^[6a]

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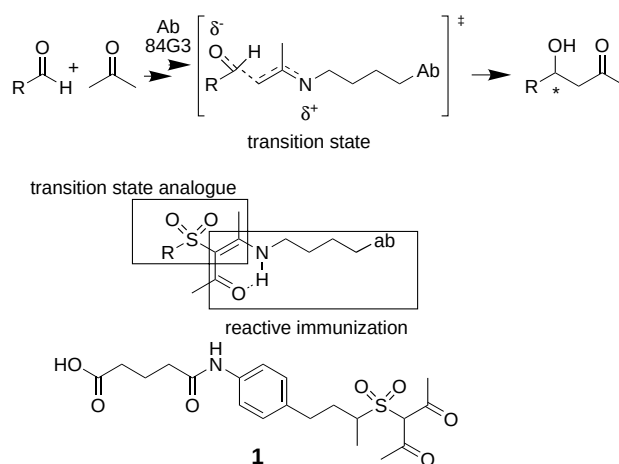
Unprecedented Regiocontrol Using An Aldolase I Antibody**

Virginie Maggiotti, Marina Resmini, and Véronique Gouverneur*

Dedicated to Professor Guy Ourisson

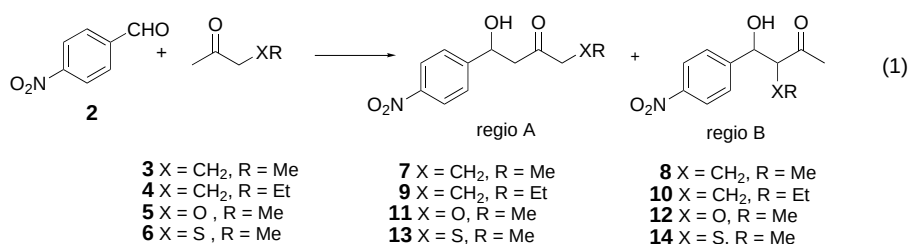
The aldol reaction is one of the most powerful methods for forming carbon–carbon bonds.^[1] The value of the reaction relies upon the degree of regio-, diastereo-, and enantioselectivity that one could control. The two approaches towards catalytic asymmetric aldol reactions are biocatalysis and chemical catalysis with Lewis acids, Lewis bases, or small molecules.^[2] Each has specific

advantages and limitations and they should thus be regarded as complementary. By combining reactive immunization and transition state analogy into a single hapten, the groups of Lerner and Barbas developed a series of aldolase antibodies which use the enamine mechanism of natural occurring class I aldolases.^[3] Here we report our findings that antibody 84G3 (ab84G3) raised against the β -diketo sulfone hapten **1**^[4] (Scheme 1) is an effective asymmetric catalyst for the regio- and enantiocontrolled formation of a series of disfavored aldol products, therefore controlling reactivity in a unique way.



Scheme 1. Mechanism of the antibody-catalyzed aldol reaction (top) and reactive immunization with **1** for the generation of ab84G3 (bottom).

An inherent challenge to the use of unmodified unsymmetrical ketones in cross aldol reactions is the control of the regioselectivity. To study the regioselectivity of the cross aldol reaction in the presence of ab84G3, *para*-nitrobenzaldehyde **2** was chosen as the standard acceptor aldehyde [Eq. (1)]. As



can be seen from Table 1, the unsymmetrical aliphatic ketones **3**–**6** undergo the aldol coupling in the presence of ab84G3. Analysis of the reaction mixtures by high-performance liquid chromatography (HPLC) indicated that in each case the antibody-catalyzed reaction occurred exclusively at the less substituted carbon atom (products **7**, **9**, **11**, **13**), independently of the presence of heteroatoms in the donor ketones. This reactivity contrasts with the results obtained for the uncatalyzed reactions carried out under the same conditions (PBS, pH 7.4, Table 1). Indeed, the uncatalyzed reactions occurred preferentially at the more substituted carbon atom resulting in a mixture of *syn* and *anti* stereoisomers (products **8**, **10**, **12**, **14**). The other regioisomer is not observed or is formed only as a minor product.

[*] Dr. V. Gouverneur, V. Maggiotti
University of Oxford
The Dyson Perrins Laboratory
South Parks Road, Oxford OX13QY (UK)
Fax: (+44)1865-275-644
E-mail: veronique.gouverneur@chem.ox.ac.uk
Dr. M. Resmini
Queen Mary, University of London
Department of Chemistry
Mile End Road, London E1 4NS (UK)

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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. Aldol reactions of *para*-nitrobenzaldehyde **2** with unsymmetrical ketones **3–6** at pH 7.4 (phosphate-buffered saline, PBS) [Eq. (1)].

Entry	Ketone	Conditions	Conversion [%] ^[a]	Ratio [%] ^[a]
1	3	RT, 3 h	0	0/0
2	3	9 mol % ab84G3, RT, 3 h	88	100/0 ^[b]
3	4	RT, 26 h	1	0/100
4	4	9 mol % ab84G3, RT, 26 h	66	99/1 ^[b]
5	5	RT, 15 h	54	4/96
6	5	0°C, 41 h	0	0/0
7	5	25 mol % ab84G3, 0°C, 41 h	76	100/0 ^[b]
8	6	RT, 3 h	49	0/100
9	6	0°C, 1 h 40 min	9	10/90
10	6	25 mol % ab84G3, 0°C, 1 h 40 min	58	98/2 ^[b]

[a] Assigned by HPLC. [b] Regio A/regio B [see Eq. (1)] as a mixture of *syn* and *anti* isomers. [b] Uncorrected ratio.

Previous studies in which other aldolase antibodies were used showed that, in the reaction with unsymmetrical ketones like 2-butanone and 2-pentanone, these antibodies exhibit some control of the regioselectivity of the aldol addition by preferential formation of the most substituted enamine.^[5] In addition, it is reported that α -heteroatom-substituted ketones like α -hydroxyacetone show a much higher level of regioselectivity with reactions occurring almost exclusively at the carbon atom bearing the oxygen atom.^[6] Aldol reactions with the unsymmetrical, sulfur-containing ketone **6** in the presence of aldolase I antibodies or enzymes have not been reported.^[7] Chemically, it is known that aldol couplings of ketone **6** with aldehydes always proceed preferentially at the carbon atom bearing the sulfur atom.^[8] Antibody 84G3 is unique in the sense that it is capable of reversing the regioselectivity for all these reactions. The regioselectivity was proven unambiguously by carrying out all the reactions under conditions that suppress any background reaction and assigned by comparison of the HPLC retention times of the products with those of independently chemically synthesized standards.^[9]

To gain more detailed information about this unusual reactivity, several aldol and retro-aldol reactions were chosen for further characterization. The kinetic experiments were all performed at room temperature and the results are collected in Table 2. For the aldol condensations (entries 1 and 2), the reactions were performed under pseudo-first order conditions by keeping the concentration of the ketones constant and in large excess. Initial rates (v_i) were determined by monitoring the formation of the products by HPLC. The adherence of the uncorrected initial rate (v_i) versus $[S]_0$ data (S = substrate) to the Michaelis–Menten equation was verified by the linearity of the $[S]_0/v_i$ against $[S]_0$ plot for both aldol and retro-aldol reactions. Determination of $k_{\text{cat}}/k_{\text{uncat}}$ was not possible for the forward aldol reactions because in the uncatalyzed reactions,

Table 2. Kinetic parameters for selected antibody-catalyzed aldol and retro-aldol reactions.

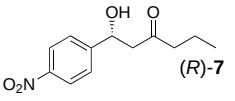
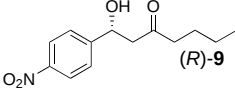
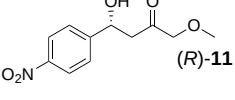
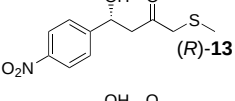
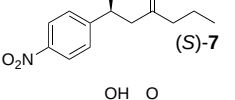
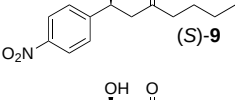
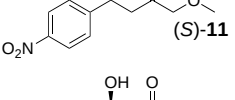
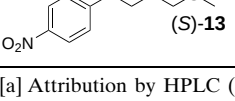
Entry	Substrates	k_{cat} [min ⁻¹]	K_m [μM]	$k_{\text{cat}}/k_{\text{uncat}}$	$(k_{\text{cat}}/K_m)/k_{\text{uncat}}$ [M ⁻¹]
1	5 + 2	0.040 (± 0.001)	390 (± 23)	–	–
2	6 + 2	0.089 (± 0.001)	217 (± 7)	–	–
3	($\pm$)- 11	0.099 (± 0.004)	170 (± 14)	5.5×10^4	3.2×10^8
4	($\pm$)- 13	0.810 (± 0.02)	69 (± 3)	4.3×10^5	6.2×10^9

the formation of regioisomer A was negligible under our assay conditions. The failure to form the regioisomer resulting from a reaction on the less substituted carbon atom in the absence of the antibody illustrates the potential of ab84G3 to catalyze an otherwise undetectable reaction.

For the antibody-catalyzed retro-aldolization of the racemic substrates ($\pm$)-**11** and ($\pm$)-**13** the kinetic results are shown in entries 3 and 4 of Table 2. The catalytic proficiencies [k_{cat}/K_m]/ k_{uncat} compare favorably with the efficiency of aldolase antibodies for other retro-aldol reactions.^[3] All antibody-catalyzed aldol and retro-aldol reactions were inhibited by the addition of an equimolar amount of 2,4-pentanedione. Further control experiments were carried out using bovin serum albumin (BSA). No catalysis of the aldol coupling was observed for these reactions. These results are consistent with a covalent catalytic mechanism in which a reactive amine is programmed in ab84G3.

HPLC analysis on a chiral stationary phase demonstrated that the typical enantioselectivities of ab84G3-catalyzed aldol or retro-aldol reactions are greater than 94 % (Table 3). For the aldol condensation of *para*-nitrobenzaldehyde with ketones **3–6**, the aldol products (*R*)-**7**–(*R*)-**13** are formed and this reflects an attack on the *si* face of the aldehyde. For the retro-aldol reactions, HPLC analysis indicated that at approximately 50 % conversion, the isolated unconverted aldol substrates possessed the *S* configuration ((*S*)-**7**–(*S*)-**13**).

Table 3. *ee* values for antibody-catalyzed aldol and retro-aldol reactions.

Product	Method	Conversion [%]	<i>ee</i> [%] ^[a]
 (<i>R</i>)- 7	aldol		94
 (<i>R</i>)- 9	aldol		98 ^[b]
 (<i>R</i>)- 11	aldol		98
 (<i>R</i>)- 13	aldol		97
 (<i>S</i>)- 7	retro-aldol	55	97
 (<i>S</i>)- 9	retro-aldol	50	94 ^[b]
 (<i>S</i>)- 11	retro-aldol	47	97
 (<i>S</i>)- 13	retro-aldol	50	96

[a] Attribution by HPLC (Chiralcel OD or OJ column). [b] No baseline separation of the two enantiomers.

These results demonstrate that both aldol enantiomers could be accessed through aldol or retro-aldol reactions using the same antibody 84G3. In order to assign the absolute configurations, the enantiopure products were synthesized by independent chemical asymmetric synthesis for compounds **9**, **11**, and **13**.^[9] The absolute configuration of compound **7** was assigned by analogy with compound **9**.

In conclusion, we described here the first aldolase antibody, ab84G3, capable of rerouting the regioselectivity of a series of cross aldol reactions which led to the formation of the otherwise disfavored products. This new reactivity highlights the scope of the reactive immunization strategy developed by the groups of Lerner and Barbas for catalyst design. This work further increases the repertoire and efficiency of antibody-catalysed aldol reactions. Further studies on the reactivity of ab84G3 are currently in progress.

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Biocatalytic Asymmetric Hydrogen Transfer**

Wolfgang Stampfer, Birgit Kosjek, Christian Moitzi, Wolfgang Kroutil,* and Kurt Faber

Driven by the increased public awareness on hazards derived from chemical production, environmentally benign oxidation methods have gained increasing importance.^[1] In this context, the reduction of ketones at the expense of a sacrificial secondary alcohol and the corresponding reverse reaction (known since the 1920s as the Meerwein–Ponndorf–Verley reduction (MPVRed) and Oppenauer-oxidation (OOx), respectively, constitute typical “green” redox reactions.^[2] As a consequence, they have been re-investigated recently^[3] to replace the previously employed metal alkoxides with catalysts showing improved efficiency,^[3c] better recoverability,^[3a] avoiding aldol condensation as side reaction,^[3f] and water-soluble analogues.^[3b] Asymmetric variants have been pursued by using enantioselective hydride-transfer methods based on chiral transition metal complexes^[3e] or chiral hydride sources.^[3a]

All biocatalytic methods for the asymmetric hydrogen transfer are based on alcohol dehydrogenases requiring nicotinamide cofactors. They have several advantages over the chemical methods, such as 1) their intrinsic asymmetry, 2) absence of side reactions, such as aldol condensation, and 3) they operate under essentially mild reaction conditions. However, their large-scale application has been impeded by the requirement for cofactor-recycling.^[4] Since the sacrificial secondary alcohol used as cosubstrate (for MPVRed) or the carbonyl compound (for OOx) has to be employed in excess to drive the reaction from equilibrium towards completion, cosubstrate inhibition is common in such a “coupled-substrate” approach based on the use of a single enzyme.^[5] Although this drawback has been surmounted to some extent by using a second dehydrogenase, which is highly specific for the sacrificial cosubstrate,^[6] these so-called “coupled-enzyme” methods are rather complex and require the handling of isolated enzymes and cofactor(s). As a consequence, biochemical MPVReds and OOxs on a large scale are limited by the use of fermenting cells^[7] and/or low (co)substrate concentration(s).^[8]

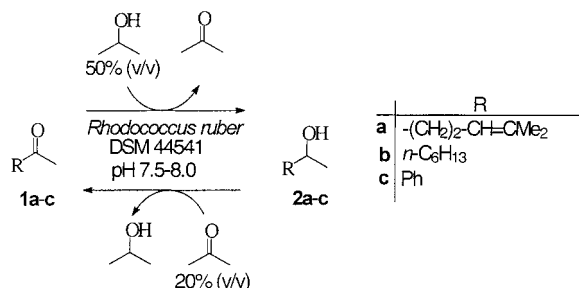
We have recently isolated a highly enantioselective secondary-alcohol dehydrogenase^[9] from *Rhodococcus ruber* DSM 44541, which is exceptionally stable towards organic solvents. The activity of the enzyme remains high at concentrations of up to 20 % (v/v) acetone and 50 % (v/v) 2-propanol. This activity enables the use of the enzyme for MVRed and OOx in the “coupled-substrate” approach. For preparative-

[*] Dipl.-Ing. Dr. W. Kroutil, Dipl.-Ing. W. Stampfer, Mag. B. Kosjek, C. Moitzi, Prof. Dr. K. Faber
Department of Chemistry, Organic and Bioorganic Chemistry
University of Graz
Heinrichstrasse 28, 8010 Graz (Austria)
Fax: (+43) 316-380-9840
E-mail: Wolfgang.Kroutil@uni-graz.at

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scale applications, whole lyophilized or resting cells can be used as a readily available alternative.

Reduction mode: Whole lyophilized cells of *Rhodococcus ruber* DSM 44541^[10, 11] grown on a standard medium (glucose, peptone, yeast extract) without enzyme induction catalyzed the reduction of **1a** in aqueous buffer at pH 7.5 with excellent enantioselectivity to furnish (*S*)-sulcatol (**2a**; Scheme 1) with



Scheme 1. Biocatalytic oxidation/reduction of secondary alcohols/ketones employing lyophilized cells in buffer and cosubstrate [20% (v/v) acetone/ 50% (v/v) 2-propanol].

an *ee* value of >99%, while the reaction was driven towards completion by addition of 2-propanol. When the cosubstrate concentration was gradually increased,^[12] the reaction rate reached a maximum at 50% (v/v) of 2-propanol (Figure 1).^[13] To explore the limits of the productivity of the system, the substrate concentration was varied by keeping the concentration of 2-propanol at a constant level of 50% (v/v). A broad optimum for the substrate concentration was found within a range of 0.5 to 1.0 mol L⁻¹, which corresponds to 76 g L⁻¹ to 126 g L⁻¹ for this substrate (Figure 1).^[14, 15]

The flexibility of this system was demonstrated by the reduction of substrates containing an aromatic moiety or α,β -unsaturated ketones (Table 1) to furnish the corresponding alcohol with excellent *ee* values.

A preparative-scale reaction was repeated at high substrate and cosubstrate concentration. Without further optimization,

Table 1. Results of the biocatalytic reduction of various ketones employing lyophilized whole cells of *Rhodococcus ruber* DSM 44541 with 50% (v/v) 2-propanol in buffer.

Substrate	<i>t</i> [h]	<i>ee</i> (Product) [%]	Conversion [%]
1a	22	> 99 (<i>S</i>)	70
1b	22	> 99 (<i>S</i>)	91
1c	22	> 99 (<i>S</i>)	81
3-octanone	22	97 (<i>S</i>)	79
2-decanone	22	> 99 (<i>S</i>)	65
1-cyclohexyl ethanone	22	> 99 (<i>S</i>)	92
1-(naphth-2-yl) ethanone	22	> 99 (<i>S</i>)	82
oct-3-en-2-one	96	> 99 (<i>S</i>)	67

1a (1.0 g, 125 g L⁻¹, 0.99 mol L⁻¹) was reduced at 24 °C within 24 h employing lyophilized whole cells of *Rhodococcus ruber* DSM 44541 (0.3 g) in phosphate buffer (pH 7.5, 50 mM) containing 50% 2-propanol to give (*S*)-sulcatol **2a** in 67% yield and >99% *ee*.^[16, 17]

Oxidation mode: Encouraged by these results, we examined the applicability of the system for the reverse reaction, that is, the oxidation of *rac* secondary alcohols at the expense of acetone as sacrificial cosubstrate.^[18] Indeed, whole cells of *Rhodococcus ruber* DSM 44541 exclusively oxidized the *S* enantiomer from racemic substrates *rac*-**2a**, *rac*-**2b**, and *rac*-**2c** (Table 2). The relative rate of oxidation for (*S*)-**2b** was about 55 times higher than that of (*S*)-**2c**. Optimization of the system showed that the oxidation rate for *rac*-**2c** measured at different acetone concentrations reached a maximum at 5% (v/v) of acetone (Figure 2). However, the reaction ceased before the maximum obtainable conversion of 50% (for a kinetic resolution) was reached. Complete reaction (conversion = 50%) occurred when the acetone concentration was increased to 20% (v/v), however, a reduction of reaction rate was observed, and preliminary results indicated that enzyme inhibition occurred. A compromise between a maximum reaction rate and minimum enzyme inhibition was found, the best results were obtained with an acetone concentration of 5% (v/v) at start followed by continuous addition throughout the reaction reaching a final acetone concentration of 20% (v/v).^[19]

Table 2. Results of the biocatalytic kinetic resolution by oxidation of secondary alcohols employing lyophilized whole cells of *Rhodococcus ruber* DSM 44541.

Substrate	Relative activity ^[a]	Enantioselectivity <i>E</i> ^[b] [%]	Conversion [%]	<i>ee</i> [%]
<i>rac</i> - 2a	1000	> 100	49.0	97.2(<i>R</i>)
<i>rac</i> - 2b	813	> 100	49.4	97.8(<i>R</i>)
<i>rac</i> -(<i>E</i>)-3-octen-2-ol	374	> 100	46.7	98.5(<i>R</i>)
<i>rac</i> -4-phenyl-2-butanol	338	> 100	49.7	95.7(<i>R</i>)
cyclopentanol	178	–	98.2	–
<i>rac</i> -1-(naphth-2-yl)ethanol	62	> 100	49.3	98.2(<i>R</i>)
<i>rac</i> - 2c	15	> 100	44.4	77.8(<i>R</i>)
<i>rac</i> -3-octanol	3	2.7	49.5	33.0(<i>R</i>)
<i>rac</i> -4-octanol	2.6	~1	36.9	0

[a] The relative activity for **1a** was arbitrarily set to 1000, which corresponds to 1.55 mmol transformed substrate h⁻¹ g⁻¹ lyophilized cells. [b] Enantioselectivity was calculated from *ee* values and conversion: $E = \frac{\ln[(1-c)(1-ee)]}{\ln[(1-c)(1+ee)]}$. All experiments were performed employing *Rhodococcus ruber* DSM 44541 with 20% (v/v) acetone in phosphate buffer at 24 °C and at pH 8.0.

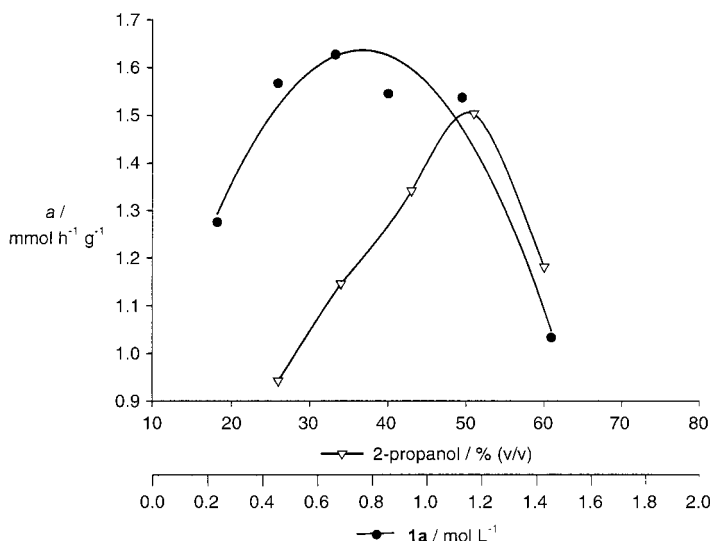


Figure 1. Activity *a* of whole cells of *Rhodococcus ruber* DSM 44541 for the reduction of **1a** in phosphate buffer (pH 7.5) at different concentrations of 2-propanol (▽) and at different substrate concentration **1a** (●, 50% (v/v) 2-propanol].

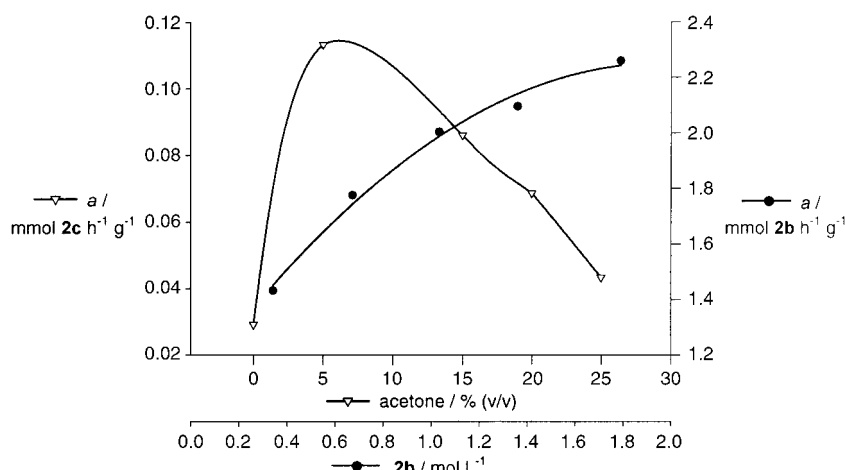


Figure 2. Activity *a* of whole cells of *Rhodococcus ruber* DSM 44541 for the oxidation of *rac*-**2c** in phosphate buffer (pH 8.0) at different concentrations of acetone (▽) and for the oxidation of *rac*-**2b** at different substrate concentration (●) at 20% (v/v) acetone.

Surprisingly, no maximum was reached when we tried to optimize the substrate concentration for *rac*-**2b** at a fixed acetone concentration of 20% (v/v) (Figure 2); the reaction rate increased continuously with increasing substrate concentration of up to 1.8 mol L⁻¹, which corresponds to 237 g L⁻¹ for *rac*-2-octanol **2b**. Beyond this value, no reliable data could be obtained as the mixture turned very viscous.

These results were confirmed on a preparative scale by kinetic resolution of *rac*-2-octanol (1.0 g, concentration 111 g L⁻¹, 0.84 mol L⁻¹) by oxidation using 0.6 g of lyophilized *Rhodococcus* cells and a final acetone concentration of 20% (v/v) in buffer at 24 °C. Within 24 h, a gas chromatography (GC) conversion of 48.8% was reached and unreacted (*R*)-2-octanol was isolated in 48% yield and 96% *ee* together with 2-octanone (37% yield).^[20] The enantioselectivity of the reaction was calculated as *E* > 100 (for a definition of *E* see Table 2).

On the one hand, *ω*-phenylalkan-2-ols and allylic alcohols, as well as cyclopentanol are very good substrates (Table 2), while secondary alkanols having a more remote hydroxy moiety in the (*ω*-2) or (*ω*-3) position are oxidized with lower activity.

To our knowledge, this is the first report of a preparative-scale biocatalytic oxidation of secondary alcohols using acetone as a cosubstrate, which is presumably because the oxidation of alcohols is thermodynamically unfavored and cosubstrate^[21] or product^[22] inhibition are common phenomena for this type of reaction. In addition, acetone is known to deactivate enzymes.

The biocatalytic redox-system described here is a simple and flexible method, at high substrate concentration, for the Meerwein–Ponndorf–Verley reduction of ketones and its reverse counterpart, the Oppenauer oxidation of secondary alcohols by a simple switch of cosubstrate. The method is highly regio- and enantioselective, and it represents essentially “clean” chemistry.

Experimental Section

Optimum of cosubstrate concentration: Cells of *Rhodococcus ruber* DSM 44541 (40 mg) were rehydrated in phosphate buffer (400 μL, 50 mM, pH 7.5

for reduction; pH 8.0 for oxidation) for 30 min at 30 °C. 2-Propanol or acetone, respectively, was added at a certain concentration. The substrate concentration was constant for all experiments (**1a**, 126 g L⁻¹; *rac*-**2c**, 18 g L⁻¹). Samples were shaken in Eppendorf vials at 130 rpm and 24 °C on a rotary shaker for 2.3 (**1a**) or 4 h (*rac*-**2c**), respectively. The reactions were quenched by addition of ethyl acetate (0.6 mL) followed by centrifugation.

The optimum for the substrate concentration for the reduction [oxidation] was determined by rehydrating whole lyophilized cells of *Rhodococcus ruber* DSM 44541 (20 mg) [30 mg] in phosphate buffer (650 μL, 50 mM, pH 7.5/reduction, pH 8.0/oxidation) for 30 min at 30 °C. 2-Propanol [acetone] was added at a concentration of 50% (v/v) [20% (v/v)]. Substrate **1a** [*rac*-**2b**] was added and the reaction shaken at 24 °C at 130 rpm for 3 h.

The enantiomeric excess was determined on a Chrom-pack Chirasil Dex column (25 m × 0.32 mm × 0.25 μm, H₂): **2a**: 80 °C isotherm, 3.4 min (S), 3.7 min (R); **2c**: 100 °C/5 min – 12 °C/min – 160 °C/0 min, 6.4 min (R), 7.6 min (S); a G-PN column (30 m × 0.32 mm, NG 9908-08, H₂) was used for the determination of **2b** as its acetate, 9.8 min (S), 10.2 min (R). The absolute configuration of (S)-**1a** and (S)-(*E*)-3-octen-2-ol was proven by comparison of the optical rotation with the literature,^[23] and that of (R)-**2b** and (R)-**2c** by co-injection with commercially available nonracemic samples on chiral GC.

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- [14] Since the solubility of most substrates in aqueous buffer is limited, apparent substrate concentrations are used throughout this study which correspond to mol substrate/total volume of the system.
- [15] The reason for the decrease of activity at high substrate concentration may be inhibition, deactivation, or limitations of the substrate transport (diffusion, transport into the cell). However, the reason was not clarified for whole cells because of the complexity of the system, but will be elucidated for the isolated enzyme.
- [16] This corresponds to a productivity of 26 mmol product h⁻¹ L⁻¹ employing 0.3 g whole lyophilized cells, or 2.3 g product g⁻¹ cells. Literature values for g product g⁻¹ whole cells for reductions are at 0.006 g g⁻¹ [7d] or 0.02 g g⁻¹ [8c].
- [17] The moderate isolated yield results from the limited half-life of whole cells at 50% (v/v) 2-propanol and may be increased by either using more cells or by starting at a lower concentration of 2-propanol [e.g. 30% (v/v)] and by continuously increasing it.
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Compartmentalization of a Gadolinium Complex in the Apoferritin Cavity: A Route To Obtain High Relaxivity Contrast Agents for Magnetic Resonance Imaging**

Silvio Aime,* Luca Frullano, and Simonetta Geninatti Crich

The search for high relaxivities continues to be a central item in the development of paramagnetic contrast agents (CA) for magnetic resonance imaging (MRI).^[1–3] This class of diagnostic agents is mainly represented by highly stable Gd^{III} chelates since the Gd^{III} ion, with its seven unpaired electrons, provides both a very high magnetic moment and a long electronic relaxation time. The observed relaxivity r_1 for the free Gd^{III} chelates may be considered as the sum of three contributions arising from the water molecule(s) directly coordinated to the paramagnetic ion (inner-sphere term),^[1, 4] from water molecules hydrogen bonded at the surface of the complex (second coordination sphere term),^[5] and from water molecules diffusing in the proximity of the complex (outer-sphere term).^[1, 4] By using the theory of paramagnetic relaxation, the design of improved systems has been pursued through the optimization of the determinants of each contribution to the overall relaxivity. However, it was found early on that the observed relaxivity could only be explained if further contributions are operative when interaction with the surface of the protein occurs. For example, the binding of GdDOTP (H₅DOTP = 1,4,7,10-tetrakis(methylenephosphonic acid)-1,4,7,10-tetraazacyclododecane), which does not contain any inner-sphere water molecules, to human serum albumin (HSA) causes a relaxation enhancement of approximately five times.^[1, 6] It was straightforward to assign such additional contributions to water molecules and exchangeable protons on the surface of the protein in the proximity of the binding site(s) of the paramagnetic complex. Clearly the microenvironment of the paramagnetic chelate is highly relevant to the determination of the relaxation-enhancing capability of a given Gd^{III} chelate. We deemed it of interest to explore new routes for the attainment of high relaxivities by exploiting such “protein surface” effects. The aim was to design systems containing a large proteic surface for interaction with the paramagnetic complex that would affect a large number of hydration water molecules and mobile protons, which, in turn, would exchange with the bulk solvent and act as amplifiers of the presence of the CA. One way to deal with a large surface is to design a spherical compartment in which the CA is trapped while the water molecules are free

[*] Prof. S. Aime, Dr. L. Frullano, Dr. S. Geninatti Crich
Dipartimento di Chimica I.F.M.
Universit  di Torino
via P. Giuria 7, 10125 Torino (Italy)
Fax: (+39) 11-670-7855
E-mail: aime@ch.unito.it

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to move in and out. Herein we report the results obtained by using a naturally occurring host molecule: apoferritin.

Ferritin consists of a spherical protein shell (apoferritin) of 24 subunits with a central cavity which can accommodate up to 4500 iron atoms in the form of a ferric oxyhydroxide crystal.^[7, 8] The central cavity is empty in apoferritin and has a diameter of 7–8 nm and an overall volume that can accommodate several contrast agent units. The access of external molecules to the inner cavity occurs through channels, formed at intersections of subunits, which are only 3–4 Å in diameter. Clearly water can diffuse through these channels, but molecules with the diameter (8–9 Å) of the currently used CA can not.^[9, 10]

A procedure for trapping small molecules inside the interior of apoferritin was previously reported.^[11] It consists first of the dissociation of apoferritin into subunits at pH 2 followed by its reforming at pH 7, thereby trapping the solution components within its interior (Figure 1). The loaded apoferritin is then separated from the molecules that are not trapped inside the shell by exhaustive dialysis. The best loading is obtained by using neutral molecules to reduce protein precipitation during the re-assembling process. Thus, among the available Gd^{III} chelates, GdHPDO3A, an extracellular contrast agent currently

used in clinical practice, was chosen. The coordination cage is very tight ($\log K_f = 23.8$) and the complex displays one coordinated water molecule (at acidic and neutral pH values) in fast exchange with the bulk water.

By following the procedure described above (Figure 1) it has been possible to entrap about 10 paramagnetic chelate units within the interior of apoferritin when the concentration of the protein and of GdHPDO3A were 1×10^{-5} M and 0.1 M,

respectively. The stability of the inclusion compound appears quite good as the relaxation rate of an aqueous solution of apoferritin loaded with GdHPDO3A did not change over several hours at ambient temperature or over one week at 4 °C. Furthermore, control experiments were carried out on the native apoferritin to check whether the CA can diffuse through the channels or can bind to the protein surface. Solutions of apoferritin (1×10^{-5} M) were incubated with GdHPDO3A (0.1 M) at room temperature for two hours and then extensively dialyzed against 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES) buffered saline. After this treatment, a relaxation rate of approximately 0.5 s^{-1} was measured, a value which is not too different from the diamagnetic contribution of the protein. This result indicates the absence of the paramagnetic complex in the solution and allows us to conclude that, under these conditions, it can not diffuse into the interior of the protein cavity nor bind to the outer surface.

The relaxivity shown by each Gd^{III} complex included in the apoferritin at 20 MHz and 298 K is very high (about $80 \pm 5 \text{ mM}^{-1} \text{ s}^{-1}$). This value is almost 20 times higher than the r_1 value of the free GdHPDO3A in water ($4.2 \text{ mM}^{-1} \text{ s}^{-1}$),^[12] and represents the highest value reported so far for systems containing one coordinated water molecule. One may argue that the observed relaxation enhancement might result from the dissociation of Gd^{III} ions during the preparative work-up and its successive coordination to the protein. This possibility has been ruled out on the basis of the following observations: 1) the proton relaxation rate does not increase, as would have been expected if Gd^{III} ions were released, when an aqueous solution containing the apoferritin and GdHPDO3A is maintained at pH 2 for more than one hour; 2) the relaxation rate of a solution of GdCl₃ (1×10^{-4} M) at pH 2 does not change upon the addition of apoferritin (1×10^{-5} M). This observation suggests that the carboxylic groups on the protein

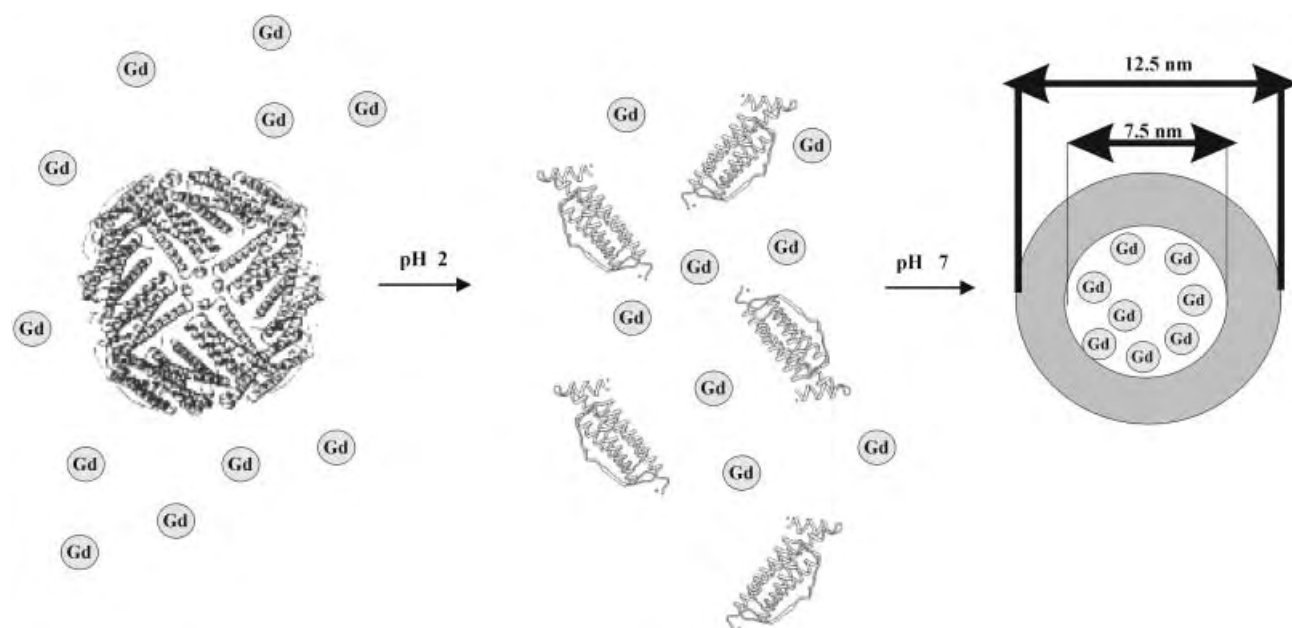
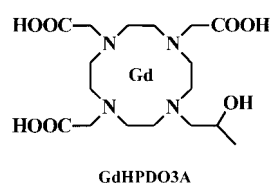


Figure 1. Schematic representation of the dissociation of apoferritin into subunits at pH 2, followed by its reforming at pH 7. In this way the solution components are trapped within its interior.

surface are protonated at pH 2 and are, therefore, unable to coordinate the Gd^{3+} ions; 3) the high-resolution ^1H NMR spectrum of EuHPDO3A recorded at pH 2 is preserved upon its entrapment within the interior of apoferritin. The Eu^{III} complex was used because the long electronic relaxation time of the Gd^{III} ion induces severe line broadening of the resonances, which prevents the recording of high-resolution spectra. On the other hand, when the pH value of a solution containing GdHPDO3A-loaded apoferritin is lowered to pH 2, the T_1 value measured after one hour is that expected for aqueous solutions of GdHPDO3A at that concentration.

The $1/T_1$ nuclear magnetic relaxation dispersion (NMRD) profile (Figure 2), recorded over a wide range of Larmor frequencies (0.01–20 MHz), shows that the GdHPDO3A-loaded apoferritin system displays high relaxivities at any field

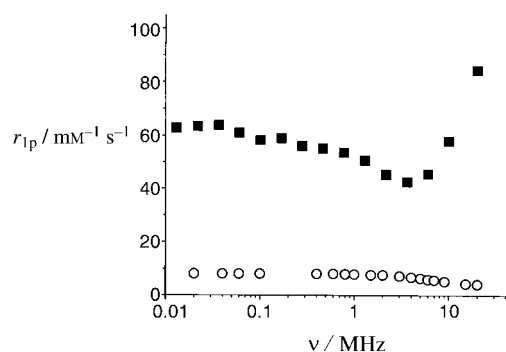


Figure 2. $1/T_1$ NMRD profiles (0.01–20 MHz) of a 1 mM solution of Gd-loaded apoferritin (■) and of GdHPDO3A (○) at pH 7 and 25 °C. ν = proton Larmor frequency, r_{1p} = relaxivity.

strength with a relaxivity hump at higher fields, as is expected for macromolecular paramagnetic adducts endowed with slow molecular reorientational times. Thus, the inclusion of several GdHPDO3A units per apoferritin cavity allows multiple interaction pathways to be established between the paramagnetic moieties, the water molecules (freely moving within the cavity or hydrogen bonded to the inner surface of the protein), and exchangeable protons, and thus yield an overall highly relaxing sink. The resulting relaxation scheme is basically the same as that occurring upon formation of protein/complex adducts, but it is now highly amplified by having a spherical surface.

Besides representing a good model for the attainment of high relaxivities, the Gd-loaded apoferritin system may have several novel applications. For example, it may be functionalized with suitable functionalities (antibody, Fab, other recognition synthons) to bind specific targeting molecules that act as reporters of given pathological states. Interestingly, an analogous approach was suggested some years ago by Hainfeld^[13] for the delivery of ^{235}U atoms to tumors. Apoferritin was loaded with an average of about 800 atoms per molecule and then Fab antibody fragments were covalently attached to the uranium-loaded apoferritin. The resulting targeting system should provide significant advantages over boronated antibodies to meet the requirements for clinical neutron-capture therapy.

Experimental Section

GdHPDO3A was kindly provided by Bracco S.p.A. Apoferritin and all other chemicals were purchased from Sigma–Aldrich (St. Louis, MO, USA).

The loading of paramagnetic chelates in the apoferritin cavity was carried out by lowering the pH value of a $1 \times 10^{-5} \text{ M}$ protein solution (1 mL) to pH 2 using 1 M HCl and maintaining this low pH value for about 15 min. After this time, when the dissociation of the apoferritin into its subunits was completed, the GdHPDO3A complex was added to the solution and the pH value was adjusted to 7.4 using 1 M NaOH. The resulting solution was stirred at room temperature for about 2 h and then exhaustively dialyzed against HEPES-buffered saline (HEPES 5 mM, NaCl 0.1 M, pH 7.4) to remove complexes not trapped inside the protein shell. The solution was then centrifuged. This operation is necessary to eliminate precipitated protein that may form during the experimental work-up. The final protein concentration was determined by the Lowry total protein micromethod assay (Sigma diagnostic). The residual GdHPDO3A concentrations were determined by inductively coupled plasma–atomic emission spectroscopy (ICP–AES). A single ICP–AES measurement represents the average of five replicates from the same sample (previously digested in nitric acid). The average value for the residual GdHPDO3A concentration was determined to be $0.0615 \pm 0.005 \text{ mM}$ from the results from four different preparations of GdHPDO3A-loaded apoferritin.

The longitudinal water proton relaxation rate was measured on a Stellar Spinmaster spectrometer (Stellar, Mede (PV) Italy) operating at 20 MHz by means of the standard inversion–recovery technique (16 experiments, 2 scans). A typical 90° pulse width was 3.5 μs and the reproducibility of the T_1 data was $\pm 0.5\%$. The temperature was controlled with a Stellar VTC-91 air-flow heater equipped with a copper–constant thermocouple (uncertainty of $\pm 0.1^\circ\text{C}$). The NMRD profile was measured over a magnetic field strength range of 0.00024 to 0.24 T (corresponding to 0.01–10 MHz) proton Larmor frequency) on a Spinmaster FFC, fast field cycling NMR relaxometer, (Stellar, Mede (PV) Italy) installed at the LIMA laboratory (Bioindustry park, Ivrea (TO), Italy). High-resolution ^1H spectra of the Eu complex were measured in D_2O with a JEOL EX-400 (400 MHz) spectrometer.

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The Asymmetric Meerwein–Schmidt–Ponndorf–Verley Reduction of Prochiral Ketones with *i*PrOH Catalyzed by Al Catalysts**

E. Joseph Campbell, Hongying Zhou, and SonBinh T. Nguyen*

The Meerwein–Schmidt–Ponndorf–Verley (MSPV) reduction of carbonyl substrates to alcohols was first reported over seventy years ago.^[1–3] It is highly chemoselective and utilizes *i*PrOH, an inexpensive hydride source.^[4] However, since the late 1950s, the classical protocol for this reduction, where Al(O*i*Pr)₃ was used as a reagent, has been largely replaced by methods using boro- and aluminum hydrides.^[5, 6] This decrease in the application of the classical MSPV reduction is partly because greater than stoichiometric amounts of Al(O*i*Pr)₃ are required to obtain satisfactory yields of the alcohol in a reasonable time.^[4] Recently, we demonstrated that the catalytic behavior of the MSPV reduction is highly dependent upon the aggregation state of the aluminum complex and if freshly made, low-aggregate aluminum alkoxides are used as catalysts, high yields of the alcohol can be achieved under mild reaction conditions.^[7]

The asymmetric MSPV-type reduction has long been prominent in synthetic methodology^[8, 9] and the Evans^[10] and Noyori^[11] groups have further improved its utility by demonstrating the stereoselective reduction of prochiral ketones using chiral variants of this reaction. These reaction variants utilize an achiral hydride source, *i*PrOH; however, they employ chiral transition metal catalysts.^[10, 11] To date, the only examples of asymmetric MSPV reduction using aluminum-based catalysts require the use of stoichiometric amounts of chiral alcohols as the hydride source.^[7, 12, 13] Herein, we report a practical, enantioselective, catalytic MSPV reduction that utilizes *i*PrOH as the hydride source and is catalyzed by AlMe₃ and enantiopure 2,2'-dihydroxy-1,1'-biphenyl [BINOL; see Eq. (1)].

On the basis of earlier precedents in aluminum aryloxide chemistry,^[14–16] we decided to combine (*R*)-(+)-BINOL and

AlMe₃ in a 1:1 ratio in toluene, and observed a white precipitate after five minutes. With the addition of a prochiral ketone (10-fold excess) and *i*PrOH (40-fold excess), the reaction medium became homogeneous [Eq. (1)]. This simple method was found to effect the catalytic reduction of 2-chloroacetophenone at room temperature to give (*R*)- α -chloromethylbenzyl alcohol in 80% *ee* and 99% yield [see Eq. (2); Table 1, entry 1]. Similarly, using (*S*)-(–)-BINOL as

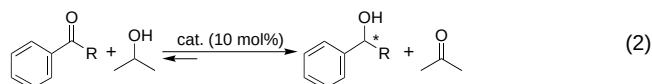


Table 1. Asymmetric MSPV reduction.^[a]

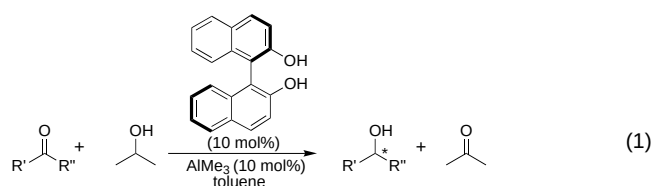
Entry	R	2-Propanol (equivalents ^[b])	Yield [%]	Product <i>ee</i> [%]
1	CH ₂ Cl	4	99	80 (<i>R</i>) ^[c]
		4	99	80 (<i>S</i>) ^[d]
2	CH ₂ Br	4	99	83 (<i>S</i>) ^[d]
		4	30	50 (<i>R</i>) ^[c]
3	CH ₂ CH ₃	15	80	46 (<i>R</i>) ^[c]
		4	32	53 (<i>S</i>) ^[d]
4	CH ₂ CH(CH ₃) ₂	15	35	35 (<i>S</i>) ^[d]
		4	20	61 (<i>S</i>) ^[d]
5	CH(CH ₃) ₂	15	46	50 (<i>S</i>) ^[d]
		4	54	30 (<i>R</i>) ^[c]
6	CH ₃	4	58	28 (<i>S</i>) ^[d]
		15	80	25 (<i>R</i>) ^[c]
7	CH ₂ OCH ₃	4	95	8 (<i>R</i>) ^[c]
		4	41	48 (<i>S</i>) ^[d]
8	acetophenone ^[e]	15	43	46 (<i>S</i>) ^[d]

[a] Reaction conditions: BINOL (0.02 mmol), AlMe₃ (0.02 mmol), ketone (0.20 mmol), and toluene (500 μ L); room temperature, N₂ for 16 h. [b] based on substrate. [c] *R* isomer obtained from reactions with (*R*)-(+)-BINOL. [d] *S* isomer obtained from reaction with (*S*)-(–)-BINOL. [e] acetophenone is the whole reactant, not an R group (not shown in Eq. (2)).

the ligand produced the (*S*)-isomer (80% *ee*, 99% yield). The enantioselective reduction of 2-bromoacetophenone also proceeds smoothly (Table 1, entry 2). The reduction of the more electron-rich substrate propiophenone can also be achieved in high yield (80%) and moderate *ee* value (46%) by the addition of excess *i*PrOH (15-fold) (Table 1, entry 3).

In general, substrates that are more sterically hindered than propiophenone lead to lower yields of the product (Table 1, entries 4 and 5), while a substrate that is less hindered gives a better yield but a lower *ee* value (Table 1, entry 6). As in the case of propiophenone (see above), a higher yield of the products can be obtained with increased *i*PrOH loading. Although α -methoxyacetophenone gives an excellent yield of the desired alcohol, the enantioselectivity is drastically reduced (Table 1, entry 7), probably because of the disruption of the tetradentate chiral intermediate (caused by the extra coordination of the MeO group, see below). Acetophenone (see Table 1, entry 8), which possesses a larger aromatic group than acetophenone, leads to higher enantioselectivity (Table 1, entry 8).

Given that the *ee* value was greatly increased by the presence of electron-withdrawing groups on the α -carbon of



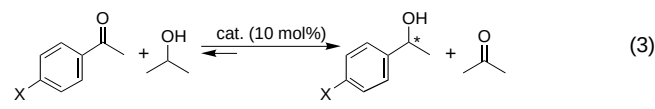
[*] Prof. Dr. S. T. Nguyen, Dr. E. J. Campbell, Dr. H. Zhou
Department of Chemistry
Northwestern University
2145 Sheridan Road, Evanston, IL 60208-3113 (USA)
Fax: (+1) 847-467-5123
E-mail: stn@chem.northwestern.edu

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

the acetophenone moiety, we decided to investigate the effect of inductive electronic parameters on the reaction shown in Equation (1). As expected, decreased electron density on the aromatic ring increases the yield of the desired alcohol.^[17, 18] However, no significant change in *ee* value was observed (Table 2).

Table 2. Electronic effect on the MSPV reduction.^[a]



Entry	X	2-Propanol (equivalents ^[b])	Yield [%]	<i>ee</i> [%]
1	H	4	54	30 (<i>R</i>) ^[c]
		15	80	25 (<i>R</i>) ^[c]
2	CH ₃	4	44	30 (<i>R</i>) ^[c]
		15	62	20 (<i>S</i>) ^[d]
3	F	4	55	30 (<i>R</i>) ^[c]
		15	55	30 (<i>R</i>) ^[c]
4	Cl	4	70	30 (<i>R</i>) ^[c]
5	Br	4	70	30 (<i>R</i>) ^[c]

[a] Reaction conditions: BINOL (0.02 mmol), AlMe₃ (0.02 mmol), ketone (0.20 mmol), and toluene (500 μ L); room temperature, N₂ for 16 h. [b] based on substrate. [c] *R* isomer obtained from reactions with (*R*)-(+)-BINOL. [d] *S* isomer obtained from reactions with (*S*)-(–)-BINOL.

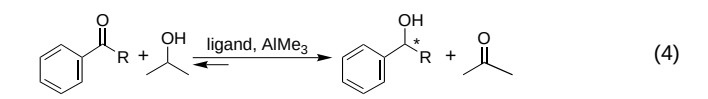
A critical characteristic of the MSPV reduction system in Equation (1) is the favorable equilibrium (both synthetically and enantioselectively) exhibited by the BINOL–Al catalyst for the monoaromatic ketone and *i*PrOH reagent pairs. Unlike previous aluminum-based asymmetric MSPV reductions, which utilized aromatic chiral alcohols as their hydride sources,^[7, 12] the enantiomeric purity of our product is maintained even after prolonged exposure to the catalyst system (see Supporting Information). After 24 h under catalytic equilibrium conditions (10 mol% (*R*)-BINOL, based on AlMe₃, 20 equivalents *i*PrOH, 20 equivalents acetone), the enantiomeric excess of a sample of chirally pure (*R*)-1-phenylethanol (98% *ee*) only decreased to 93%.

The results in Tables 1 and 2 are exciting because they indicate, for the first time, that catalytic, asymmetric MSPV

reduction of prochiral ketones can be accomplished using simple aluminum-based catalysts and an achiral hydride source. We were curious about the role of BINOL in this reaction and set out to investigate the effect of the ligand concentration and ligand binding mode, by exploring aluminum complexes of ligands **1–3** (Scheme 1).

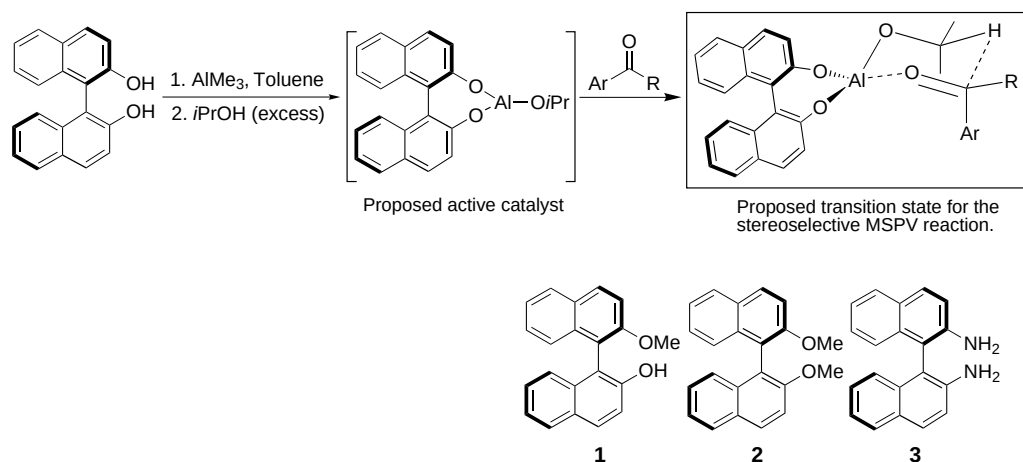
The addition of excess BINOL to the reaction in Equation (1), in which the substrate is acetophenone, does not affect the *ee* value but is detrimental to the product yield. A 1.5:1 ratio of BINOL:AlMe₃ decreases the product yield by half and a 2:1 ratio of BINOL:AlMe₃ prevents the reaction completely. The use of ligand **3** produces a very low yield of the desired alcohol (Table 3). Other primary amines, such as 2-aminopyridine and 1-(1-naphthyl)ethylamine, were also found to prevent the reaction completely. In comparison to BINOL, ligand **1** maintains the same product yield, however there is a marked decrease in the *ee* value (Table 3). Increasing the **1**:AlMe₃ ratio to 2:1 diminishes the yield of the product but does not further affect the *ee* value of the reaction. Interestingly however, with the neutral ligand **2**, which can not deprotonate before coordination to the aluminum catalyst, the yield and *ee* value of the product are significantly diminished, compared to 1 equivalent of BINOL.

Table 3. Effect of ligand additive on the MSPV reduction.^[a]



R = Me				R = CH ₂ Cl			
Ligand	Ligand:AlMe ₃	Yield [%]	<i>ee</i> [%]	Ligand	Ligand:AlMe ₃	Yield [%]	<i>ee</i> [%]
BINOL	1:1	54	30	BINOL	1:1	99	80
BINOL	2:1	0	–	BINOL	2:1	0	–
1	1:1	58	0	1	1:1	99	15
1	2:1	40	0	1	2:1	90	12
1	4:1	20	0	1	4:1	60	0
2	1:1	25	0	2	1:1	90	10
3	1:1	7	0	3	1:1	25	0

[a] Reaction conditions: ligand **1–3** (0.02 mmol), AlMe₃ (0.02 mmol), ketone (0.20 mmol), *i*PrOH (0.80 mmol), and toluene (500 μ L); room temperature, N₂ for 16 h.



Scheme 1. Proposed active catalyst and transition state for the stereoselective MSPV reaction catalyzed by [(binol)Al(OiPr)]. Ligands **1**, **2**, and **3** do not allow for an optimal MSPV geometry (a tetrahedral, four coordinate transition state) around the aluminum center.

We reported that tetradentate ligands hinder hydride transfer by aluminum catalysts.^[7] In the classical MSPV reduction, the aluminum center is believed to be tetracoordinate during the hydride transfer from one of the isopropoxide ligands to the coordinated ketone substrate.^[4] We believe that maximum *ee* value is achieved in our system when two of the aluminum alkyl groups of AlMe₃ are protonated by both phenolic protons, to form a 1:1 metal:BINOL complex during the initial catalyst formation stage. The third aluminum alkyl bond is then protonated by *i*PrOH. We believe this monomeric [(binol)(*i*PrO)Al] complex (Scheme 1) is the active chiral catalyst for this asymmetric reduction. Indeed, the use of an isolated sample of [(binol)AlMe(thf)], the THF-solvated precursor of [(binol)(*i*PrO)Al], leads to similar catalytic activity and selectivity in the reduction of α -bromoacetophenone (95% yield and 79% *ee*; see Table 1, entry 2; see Supporting Information).

A preferred requirement for the aforementioned model is that the active catalyst center is tetrahedral during the hydride transfer. Accounting for the necessary *i*PrO[−] ion and the carbonyl substrate, this model leaves only two open coordination sites for any ligand to occupy. We believe that any catalytic system in which the ligands coordinate to the metal center so as to occupy more than two coordination sites will reduce the reaction rate. The diminished activity observed when excess bidentate ligand is used (see above) supports this theory.

Increased loading of *i*PrOH shifts the equilibrium to a higher yield for the desired product, but also decreases the *ee* value (Tables 1, entries 3–6). This effect may be explained by a decrease in the effective bidentate coordination of BINOL by competing *i*PrOH coordination, thereby decreasing the *ee* value. This is a minimal factor, however, because changing from four to over 15 equivalents of *i*PrOH decreased the *ee* value at most by 5–15%, while increasing the yield by over 50% for propiophenone (Table 1, entry 3).

In summary, we have observed for the first time an asymmetric MSPV reduction that utilizes an achiral hydride source and a chiral aluminum alkoxide catalyst. A high yield was achieved using a variety of ketone substrates and a good *ee* value was obtained when the carbonyl α -carbon was sufficiently electron withdrawing.

Experimental Section

Available in the Supporting Information: General experimental procedure, quantitative analysis (including chiral gas chromatography (GC) traces), plots of conversion and *ee* value versus time for the reduction of α -bromoacetophenone, and the characterization of the proposed active chiral aluminum alkoxide catalyst (9 pages).

General MSPV Reduction Procedure: All reactions were carried out under a dry nitrogen atmosphere unless otherwise noted. Toluene (500 μ L) and enantiopure BINOL (5.8 mg, 0.02 mmol) were added to a 4-mL vial, equipped with a magnetic stirrer bar. AlMe₃ (1.9 μ L, 0.02 mmol) was added to the mixture by syringe and the reaction was stirred for 5 min, after which time a white precipitate had formed. The carbonyl substrate (10 equiv.) and 2-propanol (40 or 150 equiv.) were added, and the vial was sealed with a teflon-lined silicone septum. The reaction was stirred at room temperature under nitrogen for 16 h. Aliquots (20 μ L) were passed through a plug of neutral aluminum oxide (activated, Brockmann activity 1, ~150 mesh) and analyzed by GC to determine selectivity and conversion data (see the Supporting Information).

Scale-up Asymmetric MSPV Reduction: In the drybox, toluene (2 mL) was added to a 20-mL vial, equipped with a magnetic stirrer bar, and containing (*S*)-(−)-BINOL (57.3 mg, 0.2 mmol). AlMe₃ (19.7 μ L, 0.2 mmol) was added to the mixture by syringe and the reaction was stirred for 5 min, after which time a white precipitate had formed. α -Bromoacetophenone (0.40 g, 2.0 mmol) and 2-propanol (610 μ L, 8.0 mmol) were added and the vial was sealed with a teflon-lined cap, taken out of the drybox, and stirred at room temperature under nitrogen for 16 h. Flash column chromatography using 230–400 mesh silica gel (Merck, column dimensions = 2.5 cm $\times$ 12 cm) and CH₂Cl₂ as eluent gave a pure sample of α -(bromomethyl)benzyl alcohol, in 93% yield and 79% *ee*.

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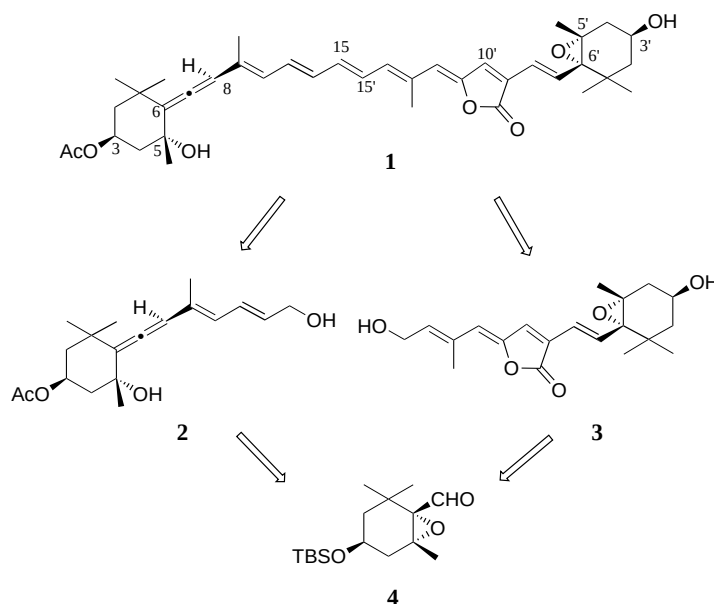
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Highly Efficient Stereocontrolled Total Synthesis of the Polyfunctional Carotenoid Peridinin**

Noriyuki Furuichi, Hirokazu Hara, Takashi Osaki, Hajime Mori, and Shigeo Katsumura*

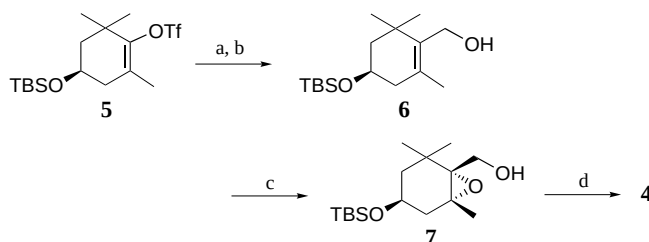
Peridinin (**1**; Scheme 1) was isolated from the planktonic algae dinoflagellates,^[1] which causes red tides, and is a carotenoid of an auxiliary light-harvesting pigment for photosynthesis in the sea.^[2] The structure of this carotenoid was determined by Lieean-Jensen and co-workers.^[3] Peridinin is a unique, highly oxidized C₃₇ nor-carotenoid that possesses an allene and a ylidenebutenolide function in the main conjugated polyene chain as well as functionalized cyclohexane rings at both ends of molecule. The synthesis of peridinin was reported by Ito and co-workers in 1993, 100 years after its isolation, and the structure of this unique carotenoid was confirmed.^[4] In that synthesis, however, control of stereochemistry and therefore yield were not considered. The stereocontrolled synthesis of peridinin presents several challenges: 1) the stereocontrolled construction of the *all-trans*-conjugated polyene chain that contains the (*Z*)- γ -ylidenebutenolide moiety and the asymmetric allene function, and 2) the stereocontrolled construction of the oxygen functions at the terminal cyclohexane ring. We overcame the problems caused by the instability of the conjugated polyene chain by effectively utilizing our own and/or new synthetic methods in a highly efficient total synthesis of peridinin. The stereochemistry of the six asymmetric carbons and the geometry of six of the seven double bonds in the molecule were controlled.

In the retrosynthetic analysis of peridinin (**1**), we bisected this molecule at the central C15–C15' double bond (carotenoid numbering). The molecule was thus divided into an allene segment **2** and a ylidenebutenolide segment **3** (Scheme 1). An important intermediate for the syntheses of both segments was the chiral epoxyaldehyde derivative **4**. Complete stereocontrol at the C3, C5, and C6 positions of the terminal cyclohexane ring had not been achieved in previous syntheses of carotenoids. The stereochemistry at these stereogenic carbon atoms was controlled by finding precise reaction conditions for the Sharpless asymmetric epoxidation^[5] after



Scheme 1. Polyfunctional carotenoid, peridinin (**1**), and its precursors **2**, **3**, and **4**.

numerous trials. Enantiomerically pure allylic alcohol **6**^[6] was prepared from known vinyltriflate **5**^[4] by palladium-catalyzed methoxycarbonylation^[7] followed by LAH reduction (Scheme 2). Sharpless epoxidation of **6** was realized by the



Scheme 2. Synthesis of **4**: a) CO, [Pd(PPh₃)₄], Et₃N, MeOH, DMF, 70 °C, 15 h (97 %); b) LiAlH₄, THF, 45 °C, 20 h (87 %); c) (–)-diethyl-D-tartrate, Ti(OiPr)₄, 1.5 M TBHP in toluene, molecular sieves (4 Å), CH₂Cl₂, –20 °C, 30 min (99 %, 92 % *de*); d) (COCl)₂, DMSO, CH₂Cl₂, –78 °C, 40 min; Et₃N, 10 min (100 %). DMF = *N,N*-dimethylformamide, Tf = trifluoromethanesulfonyl, TBHP = *tert*-butylhydroperoxide.

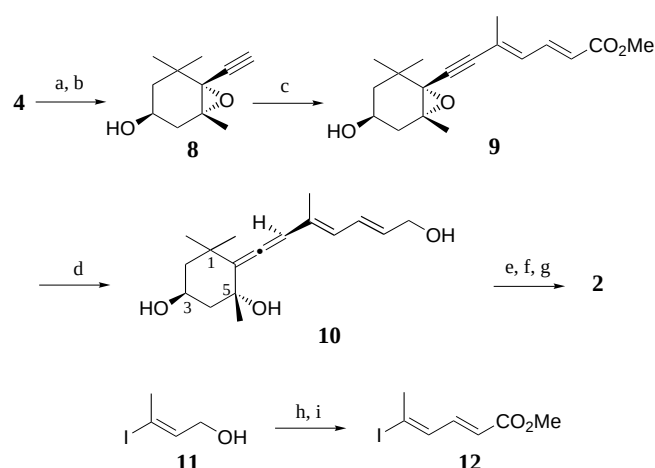
use of freshly prepared reagents, solvents and exact amounts of the reagents, ((–)-diethyl-D-tartrate (0.3 equivalents), Ti(OiPr)₄ (0.2 equivalents), and *tert*-butylhydroperoxide (2.0 equivalents)) at a constant temperature (–20 °C). Under these precise conditions, we obtained the desired α -epoxide **7** in 99 % yield and with 92 % *de*, even on a 10-g scale. The diastereoselectivity under usual conditions for the Sharpless asymmetric epoxidation was 60–70 % *de*. Epoxide **7** was transformed into epoxyaldehyde **4** by means of the Swern oxidation. This is the first example in which the stereochemistry between the C3 hydroxy group and the C5, C6 epoxide in the cyclohexane terminal of carotenoids was satisfactorily controlled.^[4, 8]

The stereocontrolled synthesis of the allene segment **2** from **4** is shown in Scheme 3. The preparation of the allylic

[*] Prof. Dr. S. Katsumura, N. Furuichi, H. Hara, T. Osaki, Dr. H. Mori
Department of Chemistry, Faculty of Science, Kwansei Gakuin
University
Gakuen, Sanda, 669-1337, Hyogo (Japan)
Fax: (+81)795-65-9077
E-mail: katsumura@ksc.kwansei.ac.jp

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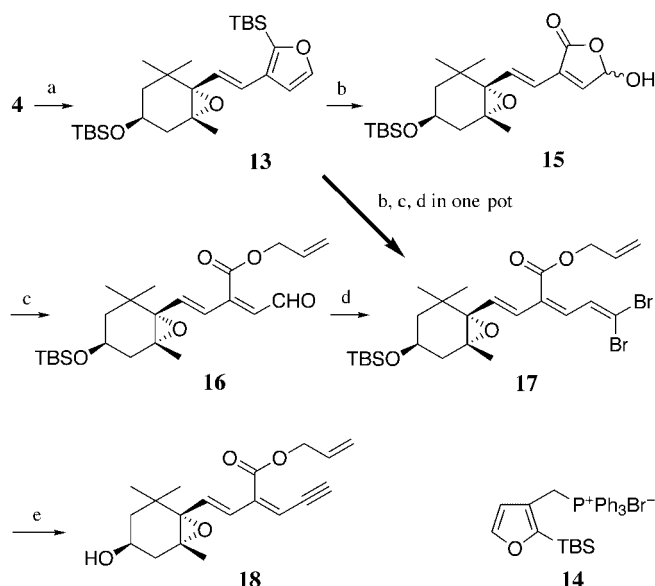
Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 3. Synthesis of **2**: a) $\text{ClCH}_2\text{P}^+\text{Ph}_3\text{Cl}^-$, $n\text{BuLi}$, THF, -30°C , 3 h; b) $t\text{BuOK}$, DMSO, room temperature, 20 min (53 % over two steps); c) **12**, $[\text{Pd}(\text{PPh}_3)_4]$, CuI , $i\text{Pr}_2\text{NH}$, room temperature, 1 h (84 %); d) DIBAL, CH_2Cl_2 , 0°C , 10 min (80 %); e) MnO_2 , diethyl ether, room temperature, 3 h; f) Ac_2O , pyridine, room temperature, 15 h (86 % over two steps); g) NaBH_4 , MeOH, room temperature 15 min (98 %); h) MnO_2 , diethyl ether, room temperature, 2 h; i) $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$, NaH , THF, room temperature, 5 min (74 % over two steps). DMSO = dimethyl sulfoxide, DIBAL = diisobutylaluminum hydride.

hydroxyallene moiety in **10** by means of $\text{S}_{\text{N}}2'$ hydride reduction^[9] of the conjugated ethynylepoxy group in **9** has been reported. We thus concentrated on the stereocontrolled preparation of **9**. The stereocontrolled construction of the conjugated polyene is the central problem in the synthesis of carotenoids, and palladium-catalyzed $\text{sp}-\text{sp}^2$ and sp^2-sp^2 is effective. Epoxyaldehyde **4** was transformed into acetylene derivative **8**.^[8] Sonogashira cross-coupling^[10] of **8** with vinyl iodide **12** (which was prepared from **11**^[11]) in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium and cuprous iodide in diisopropylamine gave the desired ester **9** in 84 % yield, with complete stereochemical control. Stereospecific $\text{S}_{\text{N}}2'$ reduction of **9** with DIBAL produced triol **10** in 80 % yield. The C3 hydroxy group was acetylated by a sequence of regioselective oxidation with MnO_2 , acetylation,^[12] and then reduction to give **2** with efficient stereocontrol.

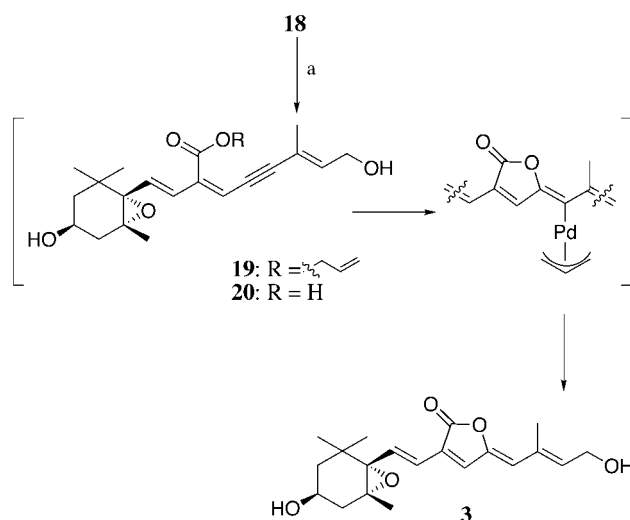
The most striking point in the synthesis of **1** was the preparation of **3**, which includes a characteristic conjugated (*Z*)- γ -ylidenebutenolide function. We have reported a highly stereoselective synthesis of the sesquiterpene freeingyne^[13] by means of a Pd^{II} -catalyzed intramolecular lactonization of a conjugated ene-yne carboxylic acid.^[14] Analogously, a conjugated ethynylcarboxylic acid such as **20** (which could be obtained from a conjugated (*Z*)- β -alkoxycarbonyldienal such as **16**, Schemes 4 and 5) could serve as a precursor of **3**. We therefore had to synthesize **16** in a stereocontrolled fashion. Thus, epoxyaldehyde **4** was treated with the ylide derived from our silylfurylmethane-Wittig salt **14**^[15] to give **13** as a single stereoisomer (Scheme 4). The silylfuran moiety of **13** was chemoselectively oxidized with $^1\text{O}_2$ ^[16] to afford the corresponding γ -hydroxybutenolide **15**. The stereocontrolled ring opening of **15** by treatment with ethyldiisopropylamine and allyl bromide in DMSO produced **16** in excellent yield. Aldehyde **16** was transformed into the relatively stable dibromide **17** by the standard method.^[17] Dibromide **17** could



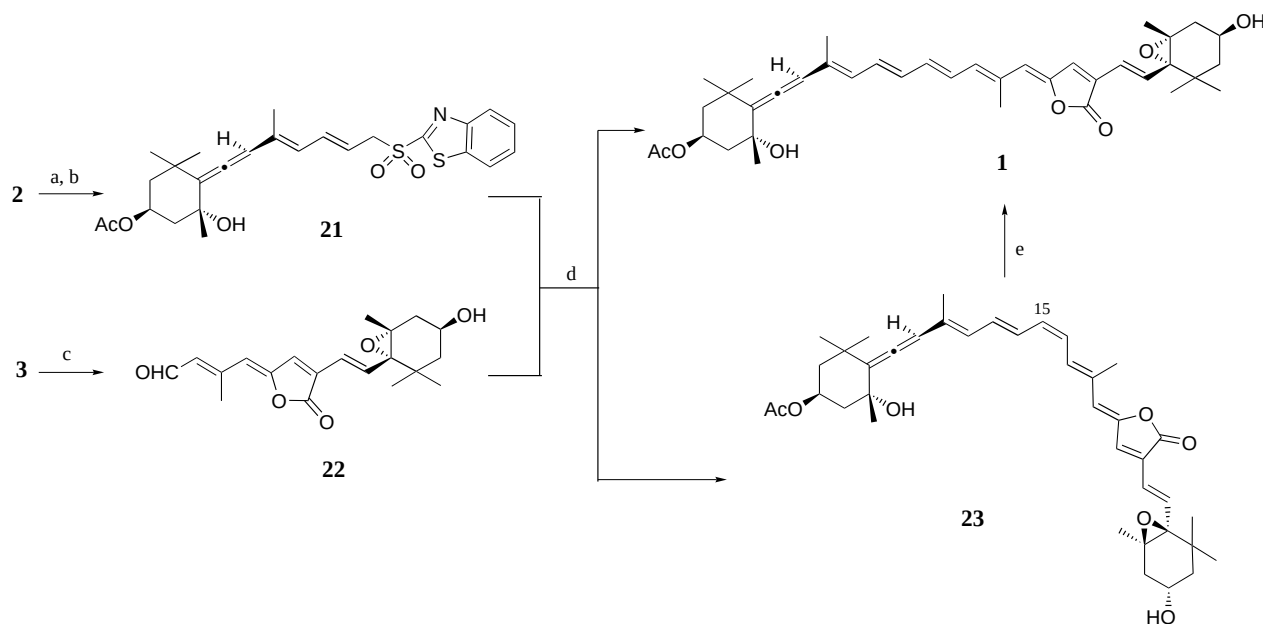
Scheme 4. Synthesis of **18**: a) **14**, $n\text{BuLi}$, diethyl ether, 0°C , 3 h; b) O_2 , TPP, CH_2Cl_2 , $h\nu$, -78°C , 30 min (77 % over two steps); c) $i\text{Pr}_2\text{EtN}$, DMSO, room temperature, 3 h, then allyl bromide, room temperature, 1 h (70 %); d) CBr_4 , PPh_3 , Et_3N , CH_2Cl_2 , -60°C , 1 h (89 %); e) TBAF, THF, 45°C , 20 h (81 %). TPP = 5,10,15,20-tetraphenyl-21 *H*,23 *H*-porphine, TBAF = tetra-*n*-butylammonium fluoride.

also be obtained from **13** in a one-pot procedure: treatment of **13** with $^1\text{O}_2$, allyl ester formation, and dibromide formation in CH_2Cl_2 gave **17** in 53 % overall yield from **4**. Dibromide **17** was transformed into **18** in 81 % yield by treatment with TBAF.^[18]

The novel and efficient one-pot stereocontrolled formation of **3** from **18** was the highlight of our synthesis (Scheme 5). A mixture of allyl ester **18** (Scheme 4) and vinyl iodide **11** (Scheme 3, 1 equivalent) was stirred in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium and cuprous iodide in triethylamine at room temperature for 1 h. After the complete consumption of **18** was ascertained by TLC, formic acid was added to the reaction mixture at room



Scheme 5. Synthesis of **3**: a) **11**, $[\text{Pd}(\text{PPh}_3)_4]$, CuI , Et_3N , room temperature, 1 h; HCO_2H , room temperature, 20 h (49 %).



Scheme 6. Total synthesis of **1**: a) 2-mercaptobenzothiazole, PPh_3 , DIAD, THF, room temperature, 1.5 h (78%); b) $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$, H_2O_2 (aq. 30%), EtOH, 0°C , 1 h (89%); c) MnO_2 , diethyl ether, room temperature, 5 min; d) NaHMDS, THF, -78°C , 5 min, in the dark (50% from **22**, *E/Z* 1:3); e) C_6H_6 , 25°C , 3 d, in the dark (*E/Z* > 5:1); preparative HPLC purification. DIAD = diisopropyl azodicarboxylate, NaHMDS = sodium bis(trimethylsilyl)amide, HPLC = high-performance liquid chromatography.

temperature, and the resulting mixture was stirred for 20 h. As expected, we obtained the desired ylidenebutenolide **3** in 49% yield as a single stereoisomer. Sonogashira coupling of **18** with **11**, reductive deallylation,^[19] and highly stereoselective intramolecular lactonization proceeded successfully via **19** in one pot^[20] by the successive action of Pd^0 and Pd^{II} catalysts.

The final step in the synthesis of peridinin was the coupling of **2** and **3**. After several trials, we knew that the halides derived from the C_{17} -allene segment **2** were unstable under the reaction conditions required for the preparation of the corresponding Wittig salt, although the very similar C_{15} -Wittig salt has been reported.^[20] We thus turned our attention to the modified Julia–Kocienski olefination,^[21] which made the olefination possible at a relatively lower temperature. Allene **2** was transformed into benzothiazole sulfone **21** by the Mitsunobu reaction with 2-mercaptobenzothiazole, followed by molybdenum(vi)-catalyzed oxidation^[22] (Scheme 6). The reaction between the sulfone group of **21** and the aldehyde function of **22** (derived from **3**) proceeded successfully within 5 min by using NaHMDS at -78°C in the dark. Although the crude product obtained was a mixture of the desired *all-trans*-peridinin (**1**) and its 15-*cis* isomer **23** (1:3 based on ^1H NMR spectroscopic analysis), we found that the *Z* isomer was converted into the thermodynamically more stable *E* isomer in a solution of benzene at room temperature in the dark after 3 days (*E/Z* > 5:1 based on ^1H NMR spectroscopic analysis and analytical HPLC). The desired enantiomerically pure peridinin (**1**) was obtained after purification by means of preparative HPLC in the dark. The spectral data of the synthetic peridinin were in good agreement with those reported.^[3, 4]

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Dynamics and Energetics of Hole Trapping in DNA by 7-Deazaguanine**

Frederick D. Lewis,* Jianqin Liu, Xiaoyang Liu, Xiaobing Zuo, Ryan T. Hayes, and Michael R. Wasielewski*

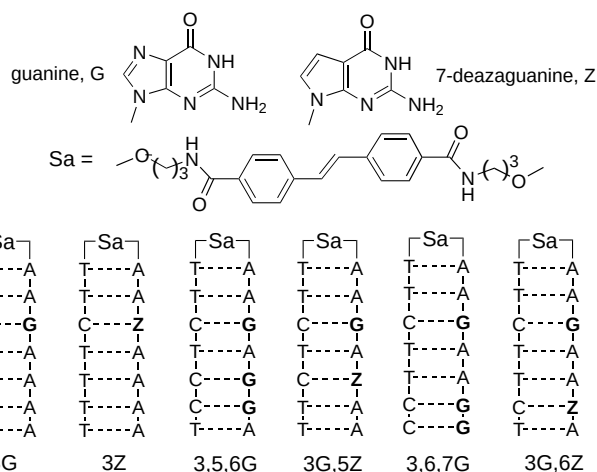
Oxidative cleavage of DNA by photonucleases can occur at sites separated from the nuclease by as many as several dozen base pairs.^[1–4] Such long-distance processes are known to occur by a multistep hole-hopping mechanism which is initiated by photoinduced electron transfer between the nuclease (electron acceptor) and a neighboring base (electron donor) resulting in creation of a hole on the base. Migration of the hole over long distances is more rapid than the chemical reactions of the oxidized bases which lead to strand cleav-

age.^[5] Strand cleavage occurs selectively at guanine, the most readily oxidized of the nucleobases, and is sequence selective.^[6, 7] Preferential cleavage at GG and GGG sequences has been attributed to stabilization of the hole by delocalization over two or three guanine residues.^[8–10]

We recently reported the use of transient absorption spectroscopy with kinetic hole modeling to obtain the rate constants for reversible hole transports between G^{•+} and GG or GGG sequences separated by a single A:T base pair.^[11, 12] The resulting Gibbs energy differences, 52 mV for GG and 77 mV for GGG, are much smaller than those previously estimated from calculations of gas-phase ionization potentials.^[8] However, recent theoretical studies by Bixon and Jortner^[13, 14] and by Kurnikov et al.^[15] have provided results in good agreement with our experimental data. Our kinetic data have also been used by Giese and co-workers^[5, 16] to model the results of strand-cleavage studies in duplexes containing G, GG, and GGG sites.

The importance of obtaining experimental values for the dynamics and energetics of hole transport in DNA led us to investigate the use of the modified nucleobase 7-deazaguanine, Z, as a hole trap. The oxidation potential of Z is reported to be 0.3 eV lower than that of G.^[17] Z has been employed in investigations of single-step (superexchange) electron transfer in DNA.^[18–20] Both Z and 8-oxoguanine, which also has a lower oxidation potential than G, have been used as hole traps in strand cleavage studies.^[6, 21] We report here the results of an investigation of the dynamics of forward and return hole transport from G to Z, which establish that Z is a much deeper hole trap than GG or GGG. In addition, the dynamics of the hole transport processes are found to be strongly dependent upon the number of A:T base pairs separating the hole donor and acceptor.

The structures of the synthetic DNA hairpins prepared for the present study are shown in Scheme 1. The stilbene-4,4'-dicarboxamide (Sa) serves as a linker connecting complementary polyT and polyA arms containing one or more C:G or C:Z base pairs.^[22] All of these hairpins have high melting temperatures (> 75 °C) and circular dichroism spectra similar to that of a stilbene-linked hairpin known to adopt a normal B-form structure in which the stilbene is parallel to the



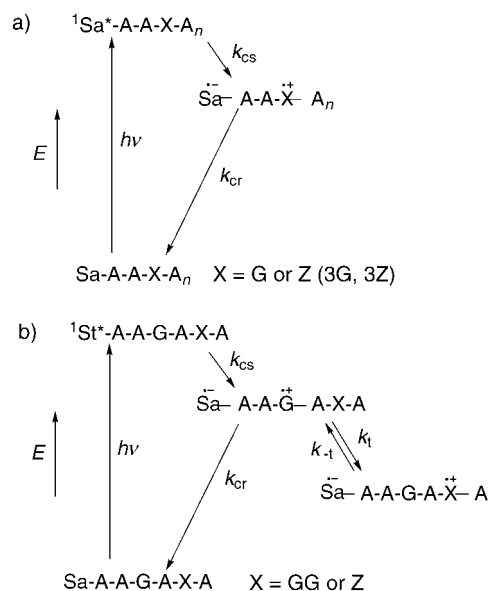
Scheme 1. Structures of the synthetic DNA hairpins used in this study.

[*] Prof. F. D. Lewis, Prof. M. R. Wasielewski, J. Liu, Dr. X. Liu, X. Zuo, R. T. Hayes
Department of Chemistry
Northwestern University
Evanston, IL 60208-3113 (USA)
Fax: (+1) 847-467-2184
E-mail: lewis@chem.northwestern.edu
wasielew@chem.northwestern.edu

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adjacent base pair.^[23] In the absence of G or Z, the Sa linker displays strong fluorescence and transient absorption spectra characteristic of the Sa singlet state ($\tau_s = 2.0$ ns). In the presence of G or Z, the fluorescence is quenched and the transient absorption displays a time-dependent change from that of $^1\text{Sa}^*$ to that of the radical anion $\text{Sa}^{\bullet-}$.^[24, 25] These changes are attributed to photoinduced charge separation resulting in the formation of $\text{Sa}^{\bullet-}$ and $\text{G}^{+\bullet}$ or $\text{Z}^{+\bullet}$ followed by charge recombination (Scheme 2a).



Scheme 2. Kinetic schemes for charge separation (k_{cs}) and charge recombination (k_{cr}) in (a) hairpins 3G and 3Z containing G or Z separated from the stilbene linker by two T:A base pairs and (b) hairpins which can also undergo hole transport (k_t and k_{-t}) from G to a more distal site containing two G or one Z residue. Only the G-containing arm of the hairpin is shown.

In the case of the hairpins 3G and 3Z, the decay of $^1\text{Sa}^*$ and $\text{Sa}^{\bullet-}$ (Table 1) can be assigned to the charge separation and charge recombination processes, respectively ($\tau_s^{-1} = k_{cs}$ and $\tau_a^{-1} = k_{cr}$).^[26] Decay of the $\text{Sa}^{\bullet-}$ transient absorption is essentially complete on the time scale of the picosecond experiment (0–6 ns). More rapid charge separation for Z than for G is attributed to more exergonic electron transfer in

the “normal” Marcus region and faster charge recombination for Z than for G to less exergonic electron transfer in the “inverted” Marcus region.^[19] Similar results have been reported by Wan et al.^[18] and by Hess et al. using other acceptors.^[20]

The hairpins 3,5,6G, 3G,5Z, 3,6,7G, and 3G,6Z possess G as the primary hole acceptor and GG or Z, respectively, as a secondary hole acceptor, separated from G by either one or two A:T base pairs (see Scheme 1). The values of τ_s for 3,5,6G, 3G,5Z, and 3G,6Z are similar to that for 3G (Table 1) in accord with their similar structures and the presence of G as the primary hole acceptor. These hairpins also have similar fluorescence quantum yields ($\Phi_f = 0.05 \pm 0.01$). Their $\text{Sa}^{\bullet-}$ transient absorption does not decay completely within the delay time limit (6 ns) of the picosecond experiment. Nanosecond transient absorption confirmed the presence of a long-lived species for each of these hairpins. In the case of 3,5,6G and 3G,5Z single exponential fits of the long-lived transient provided decay times of 170 and 6000 ns, respectively. In the case of 3G,6Z a weak, long-lived transient was observed which did not decay appreciably within 10 μs . No long-lived transient ($\tau > 5$ ns) was observed for 3,6,7G and thus the transient spectra at shorter times were not investigated.

The 170 ns decay component of 3,5,6G is attributed to charge recombination of $\text{Sa}^{\bullet-}$ with $\text{GG}^{\bullet+}$ formed by reversible hole transport from the primary G donor to the secondary GG donor (Scheme 2b).^[11, 12] In the case of 3G,5Z, reversible hole transport from G to Z plausibly is responsible for the 6000 ns decay component. Kinetic modeling of the picosecond and nanosecond transient decays according to the mechanism in Scheme 2b provides rate constants for the forward and return hole transport processes (k_t and k_{-t}). Values of k_t and k_{-t} for 3,5,6G and 3G,5Z are reported in Table 1. Comparison of the data for these hairpins reveals that k_t is significantly larger for hole transport to Z than to GG, whereas k_{-t} is smaller for Z than for GG. The ratio of forward and return hole transport rates provides the equilibrium constant and Gibbs energy difference between holes on G and Z summarized in Table 2, along with our published data for GG and GGG.^[12]

Table 2. Hole transport equilibria and thermodynamics.

Hole transport sequence	$K_{ht}^{[a]}$	ΔG_{ht} [eV] ([kJ mol ⁻¹])
$^+\text{GAZ} \rightleftharpoons \text{GAZ}^+$	1800 ± 200	0.19 ± 0.03 (18.4)
$^+\text{GAGG} \rightleftharpoons \text{GAGG}^+$ [b]	7.7 ± 1	0.052 ± 0.006 (5.0)
$^+\text{GAGGG} \rightleftharpoons \text{GAGGG}^+$ [b]	20 ± 1	0.077 ± 0.005 (7.5)

[a] Calculated from k_t/k_{-t} . [b] Data from ref. [12].

Table 1. Transient decay times and rate constants for hole transport in the DNA hairpins shown in Scheme 1.

Hairpin	τ_s [ps] ^[a]	τ_a [ns] ^[b]	k_t [s ⁻¹] ^[c]	k_{-t} [s ⁻¹] ^[d]
3G ^[e]	31 (29)	1.9 (71)		
3Z	16 (38)	1.0 (62)		
3,5,6G ^[f]	39 (35)	1.5 (50), 170 (15)	5.6×10^7	7.5×10^6
3G,5Z	37 (27)	0.82 (33), 6000 (40)	6.9×10^8	3.8×10^5
3,6,7G	not measured	< 5 ^[g]	ca. 6×10^6 ^[g]	
3G,6Z	26 (28)	1.2 (64), > 10000 (8)	5×10^7 ^[g]	< 10^5 ^[g]

[a] Stilbene singlet state decay time (preexponential). [b] Stilbene anion radical decay time(s) (preexponential). [c] Rate constant for hole transport obtained from kinetic modeling. [d] Rate constant for return transport obtained from kinetic modeling. [e] Data from ref. [25]. [f] Data from ref. [12]. [g] Estimated values, see text.

The effect of adding a second A:T base pair between the primary and secondary donors has been investigated for the hairpins 3,6,7G and 3G,6Z. The picosecond transient absorption spectrum of 3G,6Z displays a 1.2 ns component, similar in decay time to that of hairpin 3G, and a long-lived component of lower amplitude (ca. 10% of the 1.2 ns component). The nanosecond transient absorption displays only a low-amplitude component which does not decay appreciably within

10 μ s. Based on the amplitude of the long-lived component, we estimate a value of $k_t \sim 5 \times 10^7 \text{ s}^{-1}$ for 3G,6Z, a factor of 10 smaller than that for 3G,5Z (Table 1). Similar values for the attenuation of hole transport from G to GGG across multiple A:T base pairs have been reported by Meggers et al.^[27] and by Kawai et al.^[28] for hole transport from G to pyrene across multiple A:T base pairs. In the case of 3,6,7G no long-lived component is detected by means of nanosecond transient absorption. Assuming that k_t for 3,6,7G is a factor of 10 smaller than that for 3,5,6G, the resulting value of $k_t \sim 6 \times 10^6 \text{ s}^{-1}$ would be too small for the trapping to compete with charge recombination of the $\text{Sa}^{\bullet-}/\text{G}^{+\bullet}$ primary radical ion pair ($k_{\text{cr}} = 5.3 \times 10^8 \text{ s}^{-1}$). The value of k_{-t} for 3G,6Z can be estimated either from the absence of μ s decay ($k_{-t} < 10^5 \text{ s}^{-1}$) or from the value of k_t and the equilibrium constant for hole transport between G and Z in 3G,5Z ($k_{-t} \sim 3 \times 10^4 \text{ s}^{-1}$).

Comparison of our results for hole transport involving Z, GG, and GGG sites (Table 2) indicates that Z is a much deeper hole trap than either GG or GGG. The value of $\Delta G^\ominus$ for hole transport between G and Z in 3G,5Z, (-0.19 ± 0.03) eV, is smaller than either the value of -0.3 eV estimated from the irreversible oxidation potentials of dG and dZ as single nucleotides^[17] or the value of -0.39 obtained from the calculated gas-phase ionization potentials of G and Z.^[6] Base stacking is expected to lower the oxidation potentials of both dG and dZ and to exert a leveling effect on effective oxidation potentials.^[13, 14] In fact, Jortner^[29] estimates a value of $\Delta G^\ominus = (-0.14 \pm 0.03)$ eV for hole transport from G to Z, in good agreement with our experimental result.

Additional experimental data for hole trapping by Z is provided in a recent study by Nakatani et al.^[6] of the photooxidative strand cleavage reactions of duplexes containing the partial sequence 5'-GGGTTTGGG-3', where X = A, G, or Z. When X = A, photooxidation at the 5'-GGG site results in strand cleavage predominantly at that site. However, when X = G, cleavage occurs at both the 5'- and 3'-GGG sites with a ratio of 1.7:1. Little cleavage occurs at the bridging A or G. When X = Z, cleavage occurs predominantly at Z with some cleavage at the 5'-GGG site and essentially no cleavage at the 3'-GGG site. These results are consistent with hole transport rates that are smaller than that of the reaction of the 5'-GGG site with water, k_w , in the case of X = A, but larger than k_w in the case of X = G or Z. Selective cleavage at GGG versus G when X = G is consistent with equilibria which favor GGG (Table 2) and similar values of k_w for GGG and G.^[12] In the case of X = Z the equilibrium between 5'-GGG and Z favors Z by a factor of 90. Furthermore, the rate constant for hole transport from Z to 3'-GGG is expected to be $< 10^5 \text{ s}^{-1}$, the upper limit for k_{-t} across two A:T base pairs in 3G,6Z (see Table 1). This value is similar to that estimated by Giese and Spichy for the pseudo-first-order reaction of $\text{G}^{+\bullet}$ with water, $k_w \sim 6 \times 10^4 \text{ s}^{-1}$.^[5] Thus it is likely that the reaction of Z with water is faster than hole transport to G, GG, or GGG sites across two base pairs. This would account both for the absence of cleavage at the 3'-GGG site in Nakatani's investigation^[6],^[30] and for the absence of charge recombination in the transient absorption spectra of 3G,6Z.

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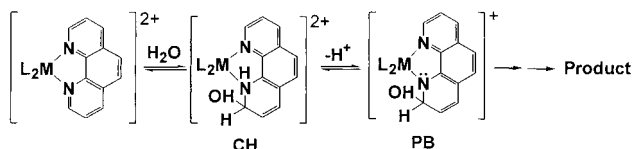
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- [30] These authors interpreted their results on the assumption that GGG forms a much deeper hole trap than Z. This explanation requires that the chemical reaction of oxidized Z be much faster than that of G.

Hydroxylation of N-Heterocycle Ligands Observed in Two Unusual Mixed-Valence Cu^I/Cu^{II} Complexes**

Xian-Ming Zhang, Ming-Liang Tong, and Xiao-Ming Chen*

Dedicated to Professor Thomas C. W. Mak on the occasion of his 65th birthday

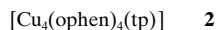
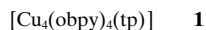
The chelate ligands 2,2'-bipyridine (bpy), 1,10-phenanthroline (phen), and their substituted derivatives have played an important role in the development of coordination chemistry,^[1, 2] and over the decades a number of so-called anomalies have been reported in reactions of their metal complexes. To rationalize the anomalous properties of complexes such as [M(bpy)₃]ⁿ⁺ and [M(phen)₃]ⁿ⁺, Gillard borrowed the idea of "covalent hydrates" from the organic literature and proposed an interesting mechanism,^[3] the core of which is nucleophilic attack of a hydroxide ion on a coordinated heterocyclic ligand to form a covalent hydrate (**CH**); this may react further by intramolecular shift of OH[−] or H₂O onto the metal before the formation of the final products (Scheme 1). The mechanism



Scheme 1. Gillard mechanism for the hydroxylation of [L₂M(phen)]²⁺. **PB** = pseudo-base.

was questioned^[4–8] because of to the lack of structural evidence^[6, 7] for the **CH** intermediate.^[8] However, if the proposed covalent hydrates of phen and bpy could be isolated as hydroxylated products, they would be novel heterocyclic ligands capable of chelating and bridging ligation for the synthesis of polynuclear metal complexes. Therefore, the hydroxylation of phen and bpy is important both in organic heterocyclic chemistry and as a possible bridge to coordination chemistry.

We report here on our observation of hydroxylated bpy and phen ligands in the two delocalized mixed-valence Cu^I/Cu^{II} complexes **1** and **2** (Hopen = 2-hydroxy-1,10-phenanthroline, Hobpy = 6-hydroxy-2,2'-bipyridine, tp = terephthalate).



[*] Prof. Dr. X.-M. Chen, X.-M. Zhang, Dr. M.-L. Tong
State Key Laboratory of Photoelectronic Materials & Technologies
School of Chemistry and Chemical Engineering,
Zhongshan University
Guangzhou 510275 (China)
Fax: (+86)20-8411-2245
E-mail: cescxm@zsu.edu.cn

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Dark brown platelike crystals of **1** and **2** (ca. 50 % yield) were obtained by heating Cu(NO₃)₂, phen or bpy, respectively, H₂tp, NaOH, and water in the molar ratio 1:1.3:0.25:0.5:1100 at 160 °C for 144 h. Both **1** and **2** are air stable and insoluble in water and most organic solvents. Maintaining the initial pH at >8 is critical to the formation of the products.

The X-ray crystal structures obtained for **1** and **2** (Figure 1) reveal unequivocally that a hydroxy group is attached at the carbon atom adjacent to a nitrogen atom (C–O 1.286(7)–1.294(7) Å) of the heterocycle ligands. There are two crystallographically independent but chemically very similar copper

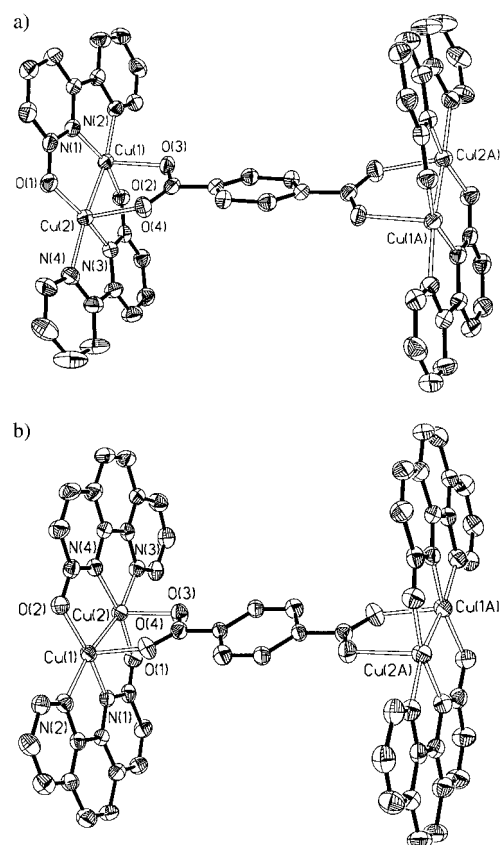
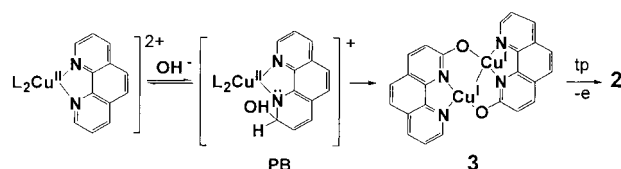


Figure 1. X-ray crystal structures of **1** (a) and **2** (b) with thermal ellipsoids set at 35 % probability. Distances of interest are discussed in the text.

atoms in **1** and **2**, as both the bond lengths and bond angles for the two metal atoms are very similar. The two metal atoms approach closely with a Cu–Cu separation of 2.415(2) Å in **1** and 2.443(2) Å in **2**. The coordination geometry of each metal atom is roughly a square pyramid composed of a pair of nitrogen atoms (Cu–N 1.950(5)–2.096(5) Å) from an obpy or ophen ligand, a deprotonated hydroxy group (Cu–O 1.921(5)–1.943(4) Å) from another obpy or ophen, and the adjacent copper atom at the equatorial positions, and by a tp carboxylate oxygen atom (Cu–O 2.167(5)–2.302(5) Å) at the apical position. The dinuclear core is somewhat similar to that found in the mixed-valence complex [Cu₂(tp)₂(4,4'-bpy)₂].^[9] The unusually short Cu–Cu distance in combination with the necessity to balance charge indicates that **1** and **2** are delocalized mixed-valence dicopper(I,II) complexes.^[9–14] A pair of the dinuclear cores is bridged to form a centrosym-

metric neutral tetranuclear Cu^{II} complex through a μ_4 -tp ligand in **1** and **2** (Figure 2).

As the Gillard mechanism suggests, hydroxylation of bpy and phen leading to Hobpy and Hophen in **1** and **2**, respectively, which was not documented previously, is the result of nucleophilic attack of hydroxide ions. In addition, we found that the formation of **1** and **2** shows significant dependence on pH (higher pH favors the formation of **1** and **2** which also indicates nucleophilic attack by a hydroxide ion on the coordinated bpy or phen during the reaction). Furthermore, our experiments^[15] confirm that coordination of bpy and phen to copper ions is critical to their hydroxylation, which is also in agreement with the Gillard mechanism. Therefore, the conversion of bpy or phen ligands into obpy and ophen during the reaction provides the structural evidence for the core of the Gillard mechanism. Based on this mechanism we propose a possible route for the formation of **1** and **2** (Scheme 2). The neutral dimeric Cu^{I} species



Scheme 2. Proposed mechanism for the formation of **2** and **3**.

$[\text{Cu}_2(\text{ophen})_2]$ (**3**) has been isolated as a by-product in the preparation of **2** and has also been structurally characterized.^[16] The existence of the Cu^{I} species suggests that some Cu^{II} ions in intermediate pseudo-base (**PB**) may act as an oxidative agent and assist the elimination of the proton on the carbon atom adjacent to the nitrogen atom. The hydroxy group is thus trapped on the aromatic ring and avoids an intramolecular shift onto the metal center. Finally, one-electron oxidation^[14] of the dinuclear Cu^{I} species, in which the oxidative agent may possibly be the remaining Cu^{II} ions, and coordination of a tp ligand as a bridge result in the formation of tetranuclear **1** and **2** comprising mixed-valence dinuclear cores (Figure 2).

Direct evidence for the mixed-valence compounds **1** and **2** also comes from the temperature-dependent magnetic susceptibility of **2**. The magnetic behavior of **2** obeys the Curie–Weiss Law in the temperature range between 2 and 200 K with an effective magnetic moment of $1.73 \mu_{\text{B}}$ per Cu_2 unit at 200 K which is consistent with one unpaired electron per dimer. A small Weiss constant of -3.71 K indicates a weak antiferromagnetic coupling of Cu_2 units either through the μ_4 -tp bridge or intermolecular $\text{Cu} \cdots \text{Cu}$ approaches. An EPR spectrum of **2** ($g = 2.10$) at 40 K shows that the paramagnetism arises from the metal centers.

It should be noted that van der Waals interactions among adjacent Cu_2^{3+} dimers are remarkable in **1** and **2**, as shown in Figure 2. Two Cu_2^{3+} dimers from neighboring molecules form a rectangle in **1** with the longer side of $4.02 \text{ \AA}$, and a parallelogram in **2** with the diagonal distance of $3.74 \text{ \AA}$ and longer side of $4.05 \text{ \AA}$. Besides, the adjacent aromatic rings of ophen and obpy stack in a face-to-face fashion with a

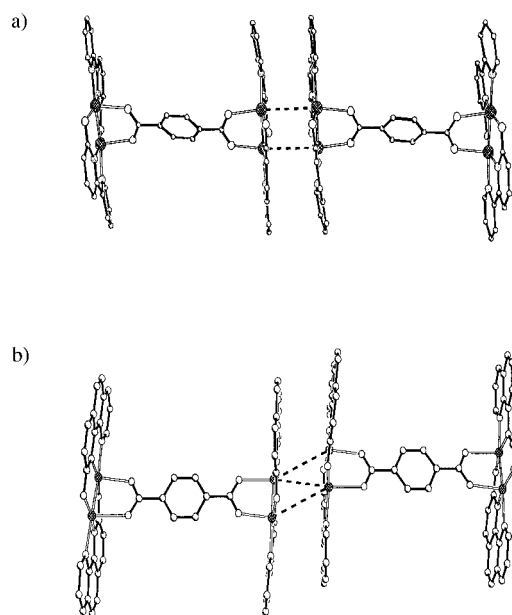


Figure 2. The intermolecular $\text{Cu} \cdots \text{Cu}$ interactions of adjacent molecules in **1** (a) and **2** (b).

separation of $3.4\text{--}3.8 \text{ \AA}$ which indicates strong $\pi\text{--}\pi$ stacking interactions between the aromatic rings. Thus, the stabilization of solids **1** and **2** may result from the intermolecular $\text{Cu} \cdots \text{Cu}$ interactions and $\pi\text{--}\pi$ stacking interaction between aromatic rings.

It is also notable that delocalized mixed-valence Cu_2 centers are important in metalloprotein systems because they involve long-distance electron transfer, and the $\text{Cu}\text{--}\text{Cu}$ bond of the Cu_2 core represents the first metal–metal bond in biology.^[17] However, up to present there have been only three approaches to stabilize model complexes containing delocalized mixed-valence Cu_2 centers: encapsulation of octaazacryptand macrobicyclic ligands, blocking of ligands, and solid-state entrapment of coordination polymers.^[9–14] Thus this work represents a new route to the stable mixed-valence dicopper complexes.

Experimental Section

A mixture of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (0.120 g), phen (0.117 g) or bpy (0.102 g), H_2tp (0.041 g), NaOH (0.02 g), and water (10 mL) in the molar ratio $1:1.3:0.25:0.5:1100$ was stirred for 20 min in air, then transferred and sealed in a 23-mL Teflon reactor, which was heated in an oven to 160°C for 144 h. The oven was cooled to room temperature at a rate of 5°C h^{-1} . The resulting dark brown platelike crystals of **1** and **2** were filtered, washed, and dried in air (yield 50%). A minor product was structurally characterized as **3** (yield ca. 3%).^[16]

1: Elemental analysis (%) calcd for $\text{C}_{24}\text{H}_{16}\text{Cu}_2\text{N}_4\text{O}_4$: C 52.27, H 2.92, N 10.16; found: C 52.16, H 2.88, N 10.03; IR (KBr, cm^{-1}): $\tilde{\nu} = 3433\text{m}$, 3070w , 1601s , 1568s , 1492s , 1458s , 1164m , 1013s , 812m , 776s , 746m , 589w ; crystal data:^[18] triclinic, space group $P\bar{1}$ (no. 2), $M_r = 551.49$, $a = 10.047(8)$, $b = 10.688(7)$, $c = 11.186(7) \text{ \AA}$, $\alpha = 79.55(1)$, $\beta = 71.76(1)$, $\gamma = 69.94(1)^\circ$, $V = 1065.9(13) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.718 \text{ g cm}^{-3}$, $\mu = 2.037 \text{ mm}^{-1}$, $F(000) = 556$; $R = 0.0667$, $R_w = 0.2101$, $\text{GOF} = 1.003$ for 308 parameters, 2655 reflections with $|F_o| = 4\sigma(F_o)$.

2: Elemental analysis (%) calcd for $\text{C}_{28}\text{H}_{16}\text{Cu}_2\text{N}_4\text{O}$: C 56.09, H 2.69, N 9.34; found: C 55.89, H 2.73, N 9.22. IR (KBr, cm^{-1}): $\tilde{\nu} = 3440\text{m}$, 3050w , 1622m , 1563s , 1511s , 1485s , 1459s , 1386s , 1365s , 1142m , 843m , 734m , 653m ; EPR: $g = 2.10$; crystal data:^[18] monoclinic, space group $P2_1/n$ (no. 14), $M_r =$

599.53, $a = 10.465(8)$, $b = 15.279(8)$, $c = 15.425(12)$ Å, $\beta = 104.60(5)^\circ$, $V = 2387(3)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 1.668$ g cm⁻³, $\mu = 1.827$ mm⁻¹, $F(000) = 1208$, $R = 0.0609$, $R_w = 0.1736$, GOF = 1.006 for 344 parameters, 2606 reflections with $|F_o| = 4\sigma(F_o)$.

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Diastereoselective Asymmetric Nitro-Aldol Reaction of α -Amino Aldehydes under High Pressure without Catalyst**

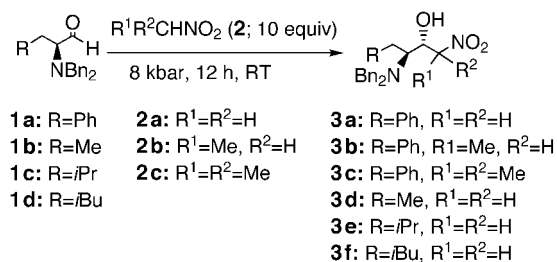
Yukihiro Misumi and Kiyoshi Matsumoto*

Dedicated to Professor Rolf Huisgen
on the occasion of his 81st birthday

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- [15] A mixture of phen (0.117 g) or bpy (0.102 g), H₂tp (0.041 g), NaOH (0.02 g), and water (10 mL) in the molar ratio 1.3:0.25:0.5:1100 was sealed in 23-mL Teflon reactor, which was heated in an oven at 160 °C for 144 h. No solid hydroxylated organic product was observed.
- [16] Crystal data for **3**: monoclinic, space group $P2_1/n$, $M_r = 517.47$, $a = 10.651(8)$, $b = 6.180(4)$, $c = 15.079(13)$ Å, $\beta = 94.160(10)^\circ$, $V = 989.9(13)$ Å³, $Z = 2$.
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The Henry (nitro-aldol) reaction is one of the most valuable methods for carbon–carbon bond formation and its stereochemical control continues to be a challenge for organic chemists.^[1–6] Specifically, an efficient synthesis of medicinally important intermediates such as phenylnorstatine through a diastereoselective catalytic (rare earth-Li-(*R*)-BINOL) asymmetric nitro-aldol reaction of optically active α -amino aldehydes with nitromethane has been reported.^[4] Tetrabutylammonium fluoride has been also used, albeit with less success.^[5] More recently, Corey and Zhang employed a rigid chiral quaternary ammonium salt for this reaction, which leads to a highly stereoselective synthesis of the HIV protease inhibitor amprenavir.^[6] More generally, nitro-aldol adducts provide ready access to non-natural 3-amino-2-hydroxy acids and 1,3-diamino-2-hydroxy units, which are substructures of medicinally important compounds.^[7, 8] One of us previously demonstrated that the Henry reaction is highly accelerated by pressure.^[9] However, to our knowledge, no attempts have ever been made to perform a diastereoselective nitro-aldol reaction without a catalyst.^[10] We envisaged that the amino group of optically active α -amino aldehydes might act as a base, and that such aldehydes would react with nitromethane under high pressure without a catalyst, thus offering a clean reaction system. Herein, we report the first example of the diastereoselective nitro-aldol reaction without any added catalyst.

N,N-Dibenzyl α -amino aldehydes **1** (Scheme 1) were chosen as a model substrate since they bear a free amino group and are relatively stable. The adducts may serve as versatile synthetic intermediates for the synthesis of non-natural

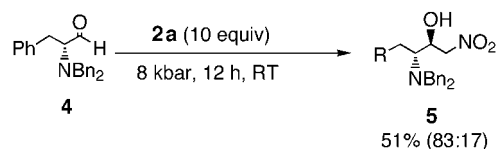


Scheme 1. Reaction of α -amino aldehydes **1** with nitroalkanes **2**.

[*] Prof. Dr. K. Matsumoto, Y. Misumi
Graduate School of Human and Environmental Studies
Kyoto University
Kyoto 606-8501 (Japan)
Fax: (+81) 75-753-2969
E-mail: kimatsu@ip.media.kyoto-u.ac.jp

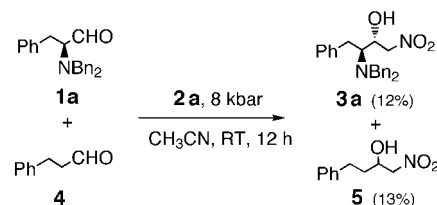
[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. The authors are also grateful to the Ministry of Education, Culture, Sports, Science, and Technology, Japan for the high-field NMR instruments (JEOL JNM-A500 and JNM-EX270) from the special fund to K.M. (1992).

3-amino-2-hydroxy acids. First, we examined the nitro-aldol reaction of (*S*)-*N,N*-dibenzylphenylalaninal (**1a**) with nitromethane (**2a**) under high pressure without a catalyst. The starting optically active α -amino aldehyde (**1a**) was prepared from the corresponding (*S*)-phenylalanine in two steps according to the procedure of Corey and Zhang.^[6] Under atmospheric pressure, **1a** did not react with **2a** (10 equiv) in acetonitrile. However, to our delight, the reaction did occur at 8 kbar (room temperature, 12 h) to give a mixture of diastereomers (*2R,3S*)-**3a** and (*2S,3S*)-*epi*-**3a** (83:17, 81 %) (Scheme 1). The mixture was purified by means of chromatography on silica gel to give a pure sample of (*2R,3S*)-**3a** and (*2S,3S*)-*epi*-**3a**. The major product (*2R,3S*)-**3a** was identified by comparison with literature data (¹H and ¹³C NMR spectroscopy).^[6] The correct choice of solvent is crucial for an efficient diastereoselective nitro-aldol reaction (Table 1, entries 1–6). Among the solvents examined thus far, CH₃CN gave the best result; the yield of **3a** decreased in the order CH₃CN > CH₃NO₂ > MeOH > CHCl₃ > CH₂Cl₂ > toluene, whereas the diastereoselectivity of **3a** decreased in the order CH₃CN > MeOH > CH₃NO₂ > CHCl₃. The optical purity was > 99 % *ee* in CH₃CN which indicates that no racemization occurred during the reaction.^[11] (*S*)-*N*-(*tert*-Butoxycarbonyl)-phenylalaninal did not react with **2a** at 8 kbar, presumably because of the lower basicity of the amino group. The reaction is quite general (e.g. Table 1, entries 7–11). The pressure and the amount of **2a** did not significantly affect the diastereoselectivity, although the yields did increase under pressure. Notably, very high diastereoselectivity was observed in the reaction of **1a** with 2-nitropropane (**2c**) (Table 1, entry 11). The diastereoselective reaction of (*R*)-*N,N*-dibenzylphenylalaninal (**4**) with **2a** produced the corresponding *anti* nitroalcohol **5** as a single enantiomer. Thus there was also no racemization in this case (Scheme 2).



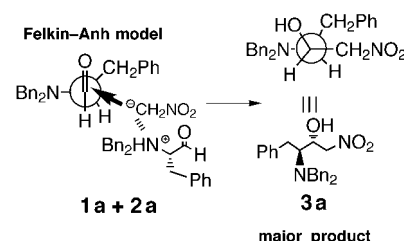
Scheme 2. Reaction of (*R*)-*N,N*-dibenzylphenylalaninal (**4**) with **2a**.

To elucidate a plausible mechanism (e.g. inter- or intramolecular), a control experiment was performed: the cross nitro-aldol reaction of **1a** (1.0 equiv) and 3-phenylpropanal (**4**) (1.0 equiv) with **2a** (1.0 equiv) was carried out under pressure (8 kbar) at room temperature, and provided a mixture of **3a** and **5** in yields of 12 and 13 %, respectively (Scheme 3).



Scheme 3. Cross nitro-aldol reaction of (*S*)-*N,N*-dibenzylphenylalaninal (**1a**) and 3-phenylpropanal (**4**) with **2a**.

A plausible mechanism for this reaction involves the initial reaction of the base **1a** with **2a** to give a carbanion. Nucleophilic attack of the carbanion at the formyl carbon atom from the *Re* face gave predominantly the *2R,3S* nitroalcohol, in agreement with the Felkin–Anh model (Scheme 4). This was further supported by the fact that the reaction of sterically hindered 2-nitropropane (**2c**) with **1a** was highly diastereoselective (Table 1, entry 11).



Scheme 4. Plausible mechanism for nitro-aldol reaction without catalyst.

In conclusion, we have presented the first diastereoselective nitro-aldol reaction without a catalyst. Although the diastereoselectivities do not rival those of reactions that require

Table 1. Diastereoselective nitro-aldol reaction of α -amino aldehydes **1** with nitroalkanes **2** without catalyst under high pressure.^[a]

Entry	Aldehyde	Nitroalkane	Solvent	Product	Yield [%] ^[b]	<i>3/epi-3</i>	<i>ee</i> (3) [%]
1	1a	2a	CH ₃ CN	3a	81	83:17 ^[c]	> 99
2	1a	2a	CH ₃ NO ₂	3a	69	74:26	98
3	1a	2a	CH ₃ OH	3a	29	78:22	96
4	1a	2a	CHCl ₃	3a	27	71:29	89
5	1a	2a	CH ₂ Cl ₂	3a	3	— ^[d]	—
6	1a	2a	toluene	3a	trace	— ^[d]	—
7	1a	2b	CH ₃ CN	3b	78	59:25:9:7 ^[c]	—
8	1b	2a	CH ₃ CN	3d	67	71:29 ^[c]	99
9	1c	2a	CH ₃ CN	3e	66 (11)	89:11 ^[c]	96 ^[f]
				3e	79 ^[g]	86:14 ^[c]	96 ^[f]
10	1d	2a	CH ₃ CN	3f	70	73:27 ^[c]	90 ^[f]
				3f	83 (4) ^[h]	85:15 ^[c]	91 ^[f]
11	1a	2c	CH ₃ CN	3c	68 (17)	99: < 1	92

[a] Reaction conditions: **1** (0.2 mmol), **2** (2.0 mmol), solvent (3 mL), 8 kbar, 12 h, room temperature. [b] Yield of isolated product, based on **1**. Values in parentheses are the amounts of **1** recovered (%). [c] Separable by chromatography. [d] Not determined. [e] The ratio was determined by means of ¹³C NMR spectroscopy. [f] The *ee* value was not accurate because of partial overlap of peaks in chiral HPLC analysis. [g] Reaction time: 24 h. [h] Reaction conditions: **1d** (0.4 mmol), **2a** (4.0 mmol), acetonitrile (2.7 mL), 8 kbar, 12 h, room temperature.

highly sophisticated catalysts,^[4, 6] the experimental procedure is extremely simple, because there is no need to quench the catalyst (see Experimental Section). Partial racemization that would result from using a catalyst is avoided. Furthermore, the use of toxic and expensive catalysts that are difficult to prepare is not necessary. This strategy, that is, pressure-mediated substrate-catalyzed reactions might also be amenable to other reactions (Michael, Mannich, Baylis–Hillman), which are accelerated by pressure.^[12] Further work along these lines is in progress.

Experimental Section

3a: A solution **1a** (66 mg, 0.2 mmol) and **2a** (108 μ L, 2.0 mmol) in acetonitrile (3 mL) was placed in a sealed Teflon vessel. The reaction mixture was stirred at room temperature under atmospheric pressure until most of **1a** had dissolved (5 min). The tube was placed in a high-pressure reactor, and pressurized to 8 kbar at 25 °C. After 12 h, the pressure was released, and the reaction mixture was transferred from the Teflon vessel into a flask. The solvent was removed under reduced pressure. The crude products were purified by means of column chromatography (SiO₂, hexane/Et₂O 10:1) to give the *anti* isomer **3a** (52 mg, 67%) and the *syn* isomer (11 mg, 14%) (total yield 81%, *anti/syn* 83:17). The enantiomeric excess was determined by means of HPLC analysis on DAICEL CHIRALCEL OJ.

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Sigmatropic Shiftamers: Fluxionality in Broken Ladderane Polymers**

Dean J. Tantillo and Roald Hoffmann*

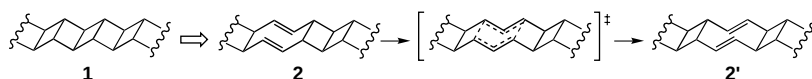
Construction principles: Consider the hypothetical ladder polymer **1**—“[∞]-ladderane.”^[1, 2] A formal [2+2] cycloreversion would lead to **2** in which a local “defect,” consisting of two parallel π bonds, is formed. Cope rearrangement via a boatlike transition structure would give **2'**, which is, of course, equivalent to **2** (Scheme 1). Continued indefinitely, this process would lead to a pair of double bonds running down the polymer chain.

[*] Prof. R. Hoffmann, Dr. D. J. Tantillo
Department of Chemistry
Baker Laboratory
Cornell University, Ithaca NY 14853-1301 (USA)
Fax: (+1) 607-255-5707
E-mail: rh34@cornell.edu

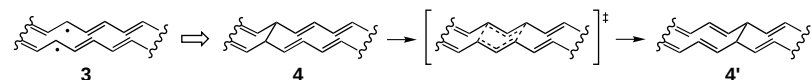
[**] We gratefully acknowledge support from the National Science Foundation (through research grant CHE 99-70089) and the National Computational Science Alliance.

Supporting information for this article (Coordinates and energies for computed structures from Scheme 2, as well as structures involved in the Cope rearrangements of **6** and **7**) is available on the WWW under <http://www.angewandte.com> or from the authors.

a) a pair of double bonds migrating down the polymer



b) a single bond migrating down the polymer



Scheme 1.

Next, consider another hypothetical system, **4**, which can be derived formally by dimerization of two neutral solitons,^[3] each on a different polyacetylene chain (**3**). Sequential Cope rearrangements in **4** would send a single bond traveling down the infinite chain (Scheme 1). One can also envisage systems in which 2, 3, or more sigma bonds are moving. Of course, the dangling chains in **4** would not stay in the requisite geometry for propagation unless they were constrained by some feat of molecular engineering. A variety of linking architectures can be envisioned, and we are currently investigating ones based on the barbaralane framework.^[4]

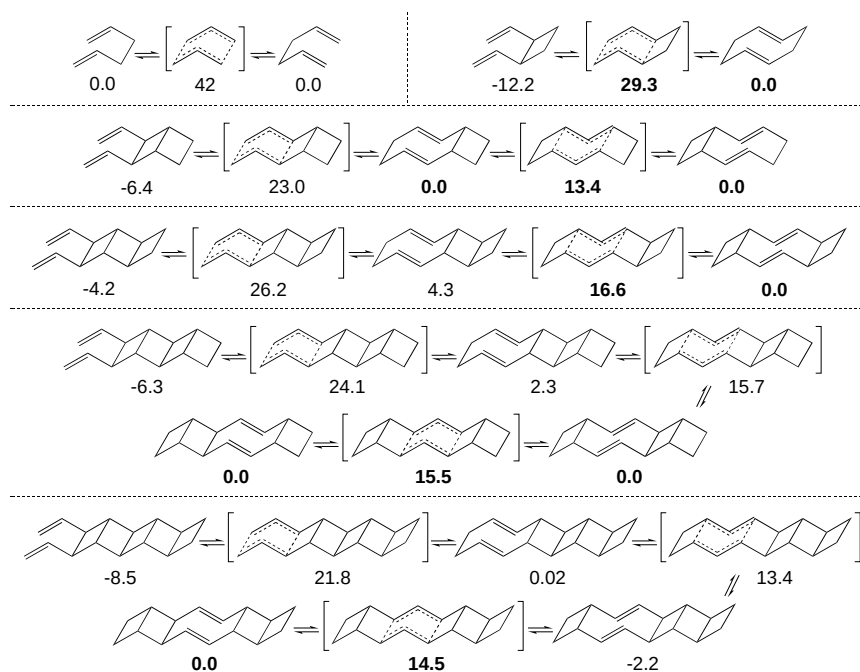
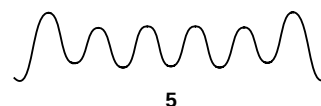
If the barriers to Cope rearrangement were low enough in these systems, **2** and **4** would be fluxional polymers. We suggest that such polymers be called “sigmatropic shiftamers”^[5] to indicate the source of their fluxionality. We describe computations on oligomeric models of **2** and related systems, which suggest that fluxionality in these shiftamers should indeed occur at room temperature.^[6]

Computational methods: All calculations were performed with the Gaussian 98 program.^[7] Geometries were optimized at the B3LYP/6-31G(d) level,^[8] which has been shown to perform well in describing structures and energetics for pericyclic reactions, including Cope rearrangements.^[9, 10] All structures were characterized by frequency calculations at the B3LYP/6-31G(d) level, and zero-point energy corrections (scaled by 0.9806)^[11] from these calculations are included in the reported energies.

Oligomeric models: Relative energies for diene isomers derived from [2]-^[10] to [7]-ladderanes and the transition structures for their interconversion are shown in Scheme 2, and the geometries of a selected “internal” diene and transition structure in Figure 1.^[12, 13] In the internal dienes, bridging cyclobutane bonds on the perimeter of cyclooctadiene substructures are consistently elongated (1.63–1.64 Å) relative to the other C–C single bonds, which range from 1.55 to 1.57 Å. The alkene carbon atoms are also significantly pyramidalized (arrow, Figure 1). These distortions lead to structures which are preorganized for Cope rearrangement.

Barriers for internal rearrangements—those that interconvert isomers containing cyclooctadiene substructures—converge to approximately 15 kcal mol^{−1} as more cyclobutanes are fused to the ends (Scheme 2).^[14, 15] This provides an estimate of the barrier for Cope rearrangement in the infinitely extended system—the shiftamer **2**. A barrier of 15 kcal mol^{−1} is low enough that fluxionality should be observable without the need for elevated temperatures. For a typical

oligomer, the potential surface will resemble that shown in **5**: a series of low internal barriers of comparable height which mimic the surface for the infinite system, flanked by higher barriers for rearrangement to the most stable isomers with terminal acyclic hexadiene substructures.



Scheme 2. Relative energies [kcal mol^{−1}] for rearrangements in oligomer models of **2**. For each system, energies are shown relative to that of the diene isomer with the innermost alkenes. Estimated barriers for the innermost Cope rearrangement in each system are highlighted in bold.

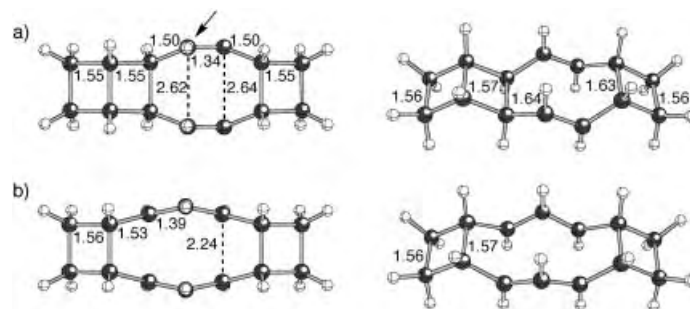
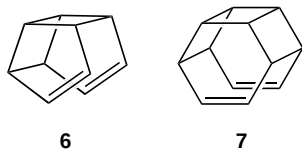


Figure 1. Selected carbon–carbon distances [Å] for a representative oligomer (a) and Cope rearrangement transition structure (b). Two views of each are shown. The arrow points to one of the highly pyramidalized alkene carbon atoms.

Running rings around: The oligomers shown in Scheme 2 extrapolate to the infinite linear polymer **2** by *trans* fusion of additional cyclobutanes. *cis* fusions produce systems that curl up on themselves and eventually “close” to discrete cyclic molecules, thereby achieving infinity through circularity.

Hypostrophene **6** (a “broken” pentaprismene) is one such molecule. Experiments indicate that **6** rearranges rapidly at



35 °C,^[16a] and our calculations predict a rearrangement barrier of 21.9 kcal mol⁻¹,^[16b] considerably larger than the barrier we predict for rearrangement in the broken ladderane polymer **2** (~15 kcal mol⁻¹).

Insertion of an additional cyclobutane ring into **6** leads to the broken hexaprismene **7**. We predict a rearrangement barrier of 25.0 kcal mol⁻¹ for **7**, again much higher than that in **2**. Although this molecule has been synthesized,^[17] it seems that its degenerate Cope rearrangement has not been observed experimentally, perhaps due to its propensity for decomposition to two molecules of benzene.

More elaborate systems can also be imagined.^[18] For example, consider the very highly strained—yet to our eyes beautiful—**8** (Figure 2), a product of multiple pentaprismene fusions, which bears the burden of multiple [2.2.2]propellane

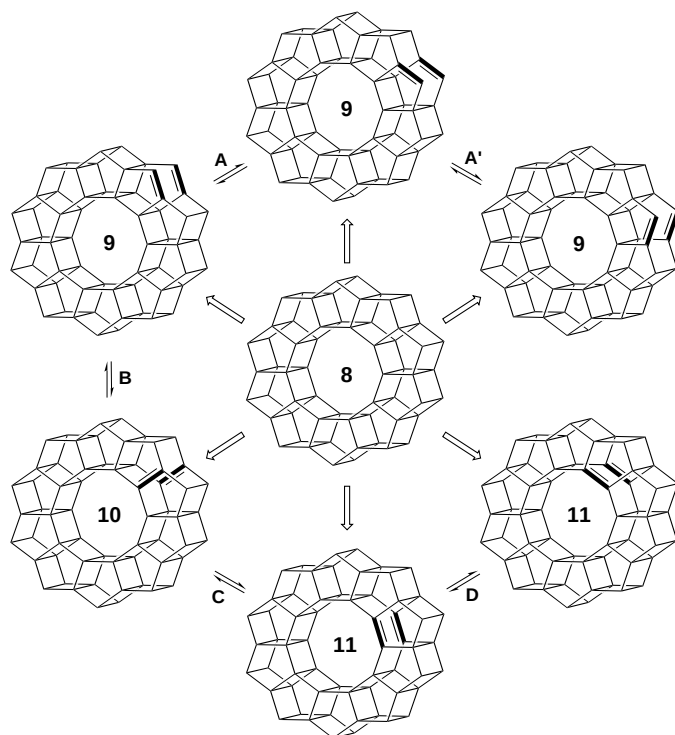


Figure 2. Hypothetical system (**8**) constructed from fused pentaprismanes. Various formal [2+2] cycloreversions in **8** lead to molecules (**9–11**) with pairs of parallel π bonds that can interconvert by various combinations of Cope rearrangements (**A–D**).

subunits. Formal [2+2] cycloreversions of various cyclobutane rings in **8** would produce a series of molecules with pairs of parallel π bonds (**9–11**). All of these isomers could, in theory, interconvert by combinations of different flavors of Cope rearrangement (**A–D**).^[19]

Conclusions: We predict that the shiftamer **2** should be fluxional at room temperature, its pair of parallel alkenes running back and forth along the polycyclobutane framework. Other sigmatropic shiftamers are currently under investigation.

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Ultrastable and Highly Acidic, Zeolite-Coated Mesoporous Aluminosilicates**

Do Trong On and Serge Kaliaguine*

The acidity and hydrothermal stability of mesoporous aluminosilicates (MesoAS) are relatively low compared to those of zeolites, which limits their potential applications as catalysts in petroleum refining and fine chemicals synthesis.^[1–7] Much effort has therefore been undertaken to synthesize a new type of materials, which combines the advantages of both zeolites and mesoporous molecular sieves. One might expect to improve both the stability and acidity of these materials if zeolite-like order could be introduced into the

mesopore walls. Recent advances showed that amorphous walls of the mesostructure could indeed be converted to a partially zeolitic product.^[8–13] For example, MCM-41/MFI composites containing interconnected mesopores and micropores were prepared by using dual templates and exhibited enhanced acidity and steam stability compared to the corresponding MCM-41.^[8, 9] Furthermore, the use of zeolite seeds as precursors for the assembly of mesoporous aluminosilicates with high hydrothermal stability and acidity was reported by Pinnavaia et al.^[10] A similar zeolite beta type of materials was also prepared in the presence of co-templates of tetraethylammonium hydroxide and cetyltrimethylammonium bromide.^[11] Recent results from our group showed the preparation of a new type of materials with semicrystalline zeolitic mesopore walls based on a templated solid-state secondary crystallization of zeolites starting from the amorphous walls of SBA-15. Bright- and dark-field transmission electron microscope (TEM) images recorded on the same area of the sample indicated that nanocrystals were embedded in the continuous amorphous inorganic matrix to form semicrystalline wall structures while preserving the mesoporous structure. The resulting mesoporous materials had much stronger acidity than those of the corresponding amorphous aluminosilicates and a much improved hydrothermal stability.^[12]

Herein, we describe a new approach for the production of unusual zeolite-coated mesoporous aluminosilicates (ZCMeso-AS) using diluted clear solutions containing primary zeolite units. Hydrothermally ultrastable and highly acidic ZCMeso-AS result owing to the nanocrystalline zeolitic nature of their pore wall surface. These features open new possibilities for using this type of materials as acid catalysts.

It is of special concern that due to the size of primary ZSM-5 units templated by tetrapropylammonium ions (2.8 nm in diameter),^[13–14] the pore diameter of the mesoporous precursor molecular sieves should be higher than 30 Å. The methods in references [2] and [3] are therefore useful in this context for the preparation of mesoporous precursors, such as SBA-15 and siliceous mesostructured cellular foams (MCFs).

The N₂ adsorption/desorption isotherms obtained from the calcined sample before and after coating are shown in Figure 1A. The parent and ZSM-5-coated samples display the typical behavior of a mesoporous molecular sieve with a mesopore volume saturation capacity of about 1.56 and 0.78 cm³ g⁻¹, respectively (Table 1). The *P*/*P*₀ position of the inflection point is related to a diameter in the mesopore range, and the sharpness of these steps indicates the uniformity of the pore size. A narrower distribution of the pore diameter of the coated sample compared to that of the parent sample was observed (Figure 1B). Furthermore, a significant decrease in pore diameter (from 70 to 54 Å) and in surface area (from 800 to 465 m² g⁻¹) could conceivably be ascribed to the ZSM-5 nanocrystals coated inside the mesopore channels of the host. Figure 2 shows a TEM image of the ZSM-5-coated MesoAS. A uniform pore size with a highly ordered structure is still observed for this sample after the coating procedure.

The ZSM-5-coated MesoAS sample shows a FTIR absorption band at 550 cm⁻¹, which is not present in the parent MesoAS sample (Figure 3). The band around 550 cm⁻¹ has been assigned to the asymmetric stretching mode in double-

[*] Prof. S. Kaliaguine, Dr. D. Trong On
Department of Chemical Engineering
Laval University
Quebec G1K 7P4 (Canada)
Fax: (+1) 418-656-3810
E-mail: kaliagui@gch.ulaval.ca

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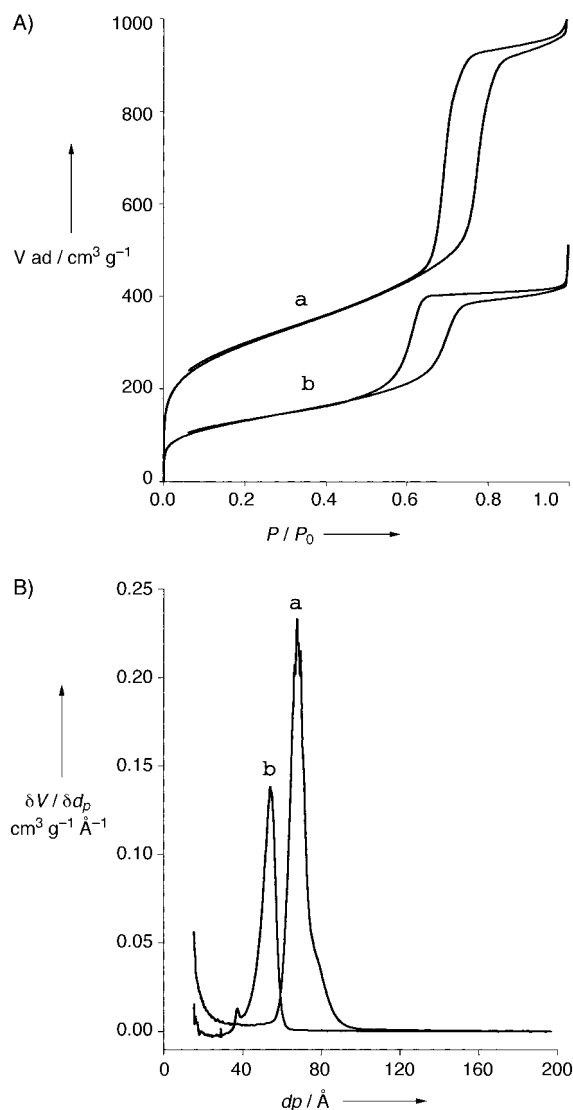


Figure 1. N_2 adsorption/desorption isotherms of nitrogen at -196°C (A) and Barrett–Joyner–Halenda (BJH) pore diameter distributions calculated from the desorption branch of the isotherm (B) for a) parent MesoAS, b) ZSM-5-coated MesoAS.

Table 1. Physicochemical properties of the parent mesoporous aluminosilicate (PMesoAS) and ZSM-5-coated mesoporous aluminosilicate (ZCMesoAS) samples.

Entry	Materials	Si/Al ^[a]	S_{BET} [$\text{m}^2 \text{g}^{-1}$]	S_{BJH} [$\text{m}^2 \text{g}^{-1}$]	Mesopore volume [$\text{cm}^3 \text{g}^{-1}$]	BJH pore diameter [$\text{\AA}$]
1	PMesoAS	65	1080	800	1.56	70
2	ZCMesoAS	50	495	465	0.78	54

[a] Atomic Si/Al ratios obtained by atomic adsorption spectroscopy.

ringblocks and is observed in all of the zeolite structures that contain the double 4-, double 5-, and double 6-rings (zeolite X, Y, A). Such a band was also assigned to the vibration associated with the five-membered ring in the pentasil secondary building units.^[10] Its occurrence indicates therefore that ZSM-5 nanocrystals are present within the mesostructured material.

The FTIR spectra of adsorbed pyridine after desorption at 150°C on the parent MesoAS (atomic Si/Al = 65/1) in H-form

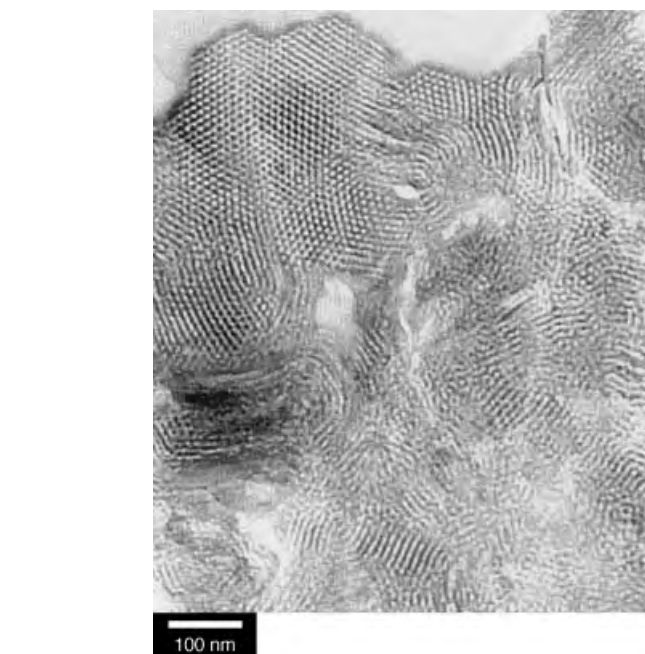


Figure 2. TEM image of ZSM-5-coated MesoAS.

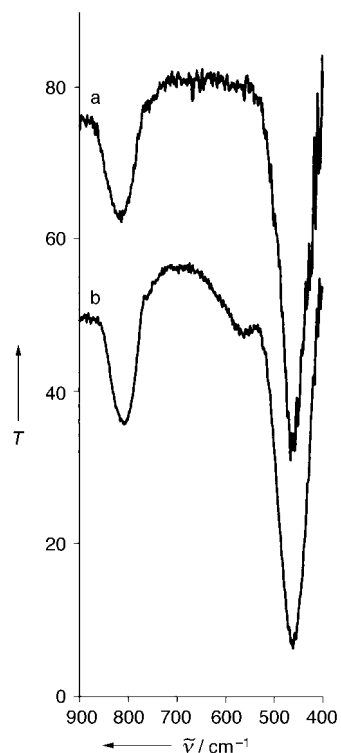


Figure 3. FTIR spectra of: a) parent MesoAS, b) ZSM-5-coated MesoAS.

and H-ZSM-5-coated MesoAS (Si/Al = 50/1) samples and on H-ZSM-5 (Si/Al = 57/1) as the reference are shown in Figure 4 (the samples in H-form were obtained by the ion exchange of Na^+ by NH_4^+ followed by calcination at 550°C). Two intense bands at 1547 and 1455 cm^{-1} , which are characteristic of Brönsted and Lewis acid sites, respectively, are observed for the H-ZSM-5-coated MesoAS sample and the H-ZSM-5 reference; however, no such bands are observed for the parent MesoAS sample in H-form. This suggests that the

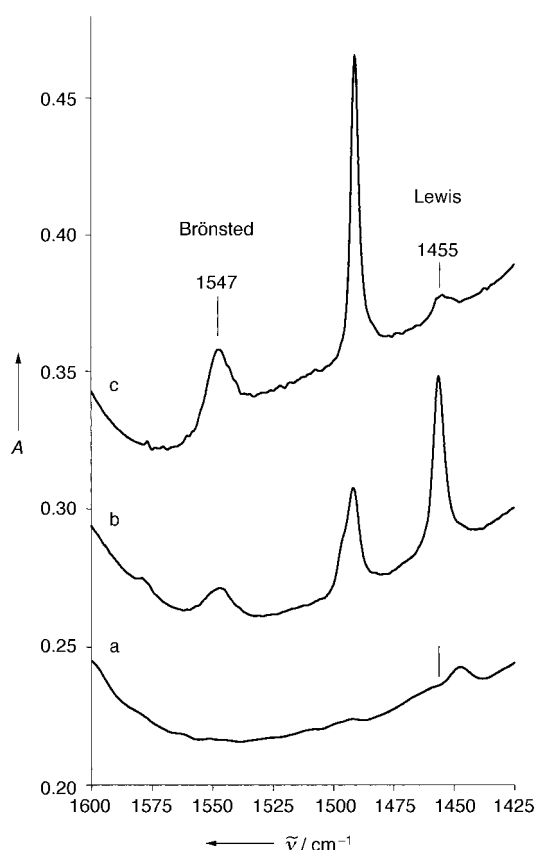


Figure 4. FTIR spectra of the adsorbed pyridine in the 1350–1600 cm^{-1} range after pyridine adsorption and then desorption at 150 °C: a) parent MesoAS in H-form, b) H-ZSM-5-coated MesoAS, c) H-ZSM-5.

acidity of the coated sample is comparable to that of the H-ZSM-5 reference with a larger fraction of Lewis acid sites and much higher than that of the parent sample. The order of the acid site density is H-ZSM-5 > H-ZSM-5-coated MesoAS $\gg$ parent MesoAS.

The ^{27}Al MAS NMR spectra of the parent MesoAS and ZSM-5-coated samples exhibit a single resonance centered at about $\delta = 56$, which is characteristic of tetrahedral aluminum centers. This indicates that most of the aluminum is incorporated into the material framework. The ^{29}Si MAS NMR spectrum of the parent MesoAS sample (atomic Si/Al = 65/1) is typical of mesoporous aluminosilicates (Figure 5); it contains four main features^[7, 15] (Figure 5a). Two main resonances at $\delta = -112$ and -100 and a weak peak at $\delta = -92$ correspond to $\text{Si}(\text{OSi})_4$ (Q^4), $(\text{HO})\text{Si}(\text{OSi})_3$ (Q^3), $(\text{HO})_2\text{Si}(\text{OSi})_2$ (Q^2) silicate species, respectively; a shoulder at $\delta = -105$ has been assigned to $(\text{AlO})_1\text{Si}(\text{OSi})_3$ species due to the tetrahedral aluminum structure. By contrast, the ^{29}Si MAS NMR spectrum of the coated sample (atomic Si/Al = 50/1) shows a main resonance centered at $\delta = -112$, which is attributed to Q^4 silicon of the silicalite framework and a shoulder $(\text{AlO})_1\text{-Si}(\text{OSi})_3$ band at $\delta \sim 105$ (Figure 5b). Only a weak resonance attributable to Q^3 silicon from surface hydroxy groups is observed at $\delta \sim 100$. The increase in intensity of the Q^4 resonance and concomitant decrease in intensity of the Q^3 and Q^2 resonances reflect the transformation of the hydrophilic surface of the precursor into a more hydrophobic one upon applying the coating procedure.

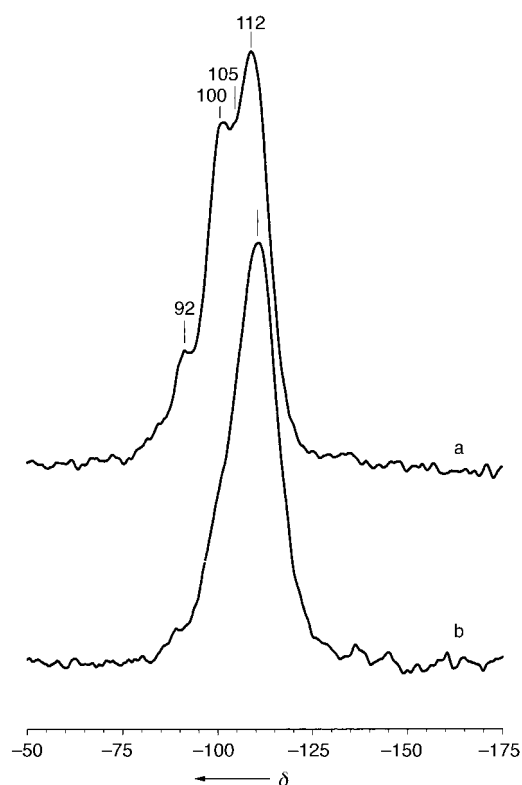


Figure 5. ^{29}Si MAS NMR spectra of: a) parent MesoAS, b) ZSM-5-coated MesoAS.

The hydrothermal stability in boiling water at 100 °C and steam stability with 20% water vapor in N_2 at 800 °C of the parent mesoporous molecular sieves (MMS) sample and the ZSM-5-coated MesoAS sample were also studied (Table 2). The pore diameter distributions of the parent MMS sample before and after treatment in boiling water at 100 °C for 48 h are shown in the inset in Figure 6A. The mesopore structure of the parent MesoAS sample had collapsed after this treatment for 48 h. By contrast, no significant collapse of the mesopore structure was observed for the ZSM-5-coated MMS sample after 48 h under the same treatment conditions. The pore volume and BJH surface area varied slightly from 0.78 to 0.85 $\text{cm}^3 \text{g}^{-1}$ and from 465 to 485 $\text{m}^2 \text{g}^{-1}$, respectively (Figure 6A); even after 120 h, the mesopore structure was

Table 2. Physicochemical properties of the parent mesoporous aluminosilicates (PMesoAS) and ZSM-5-coated mesoporous aluminosilicates (ZCMesoAS) samples before and after hydrothermal treatments.

Entry	Materials	Treatment time [h]	S_{BET} [$\text{m}^2 \text{g}^{-1}$]	S_{BJH} [$\text{m}^2 \text{g}^{-1}$]	Mesopore volume [$\text{cm}^3 \text{g}^{-1}$]	BJH pore diameter [Å]
boiling water at 100 °C						
1	PMesoAS-0-W ^[a]	0	1080	800	1.56	70
2	PMesoAS-48-W	48	415	375	1.72	120
3	ZCMesoAS-0-W	0	495	465	0.78	52
4	ZC MesoAS-48-W	48	475	485	0.85	55
5	ZC MesoAS-120-W	120	485	495	1.35	58
steaming of 20% vapor water in N_2 at 800 °C						
6	ZCMesoAS-24-S	24	445	400	0.70	53

[a] PMesoAS-*x*-*y* where: *x* treatment time in hours, *y*: boiling water (W) or steaming (S) treatment.

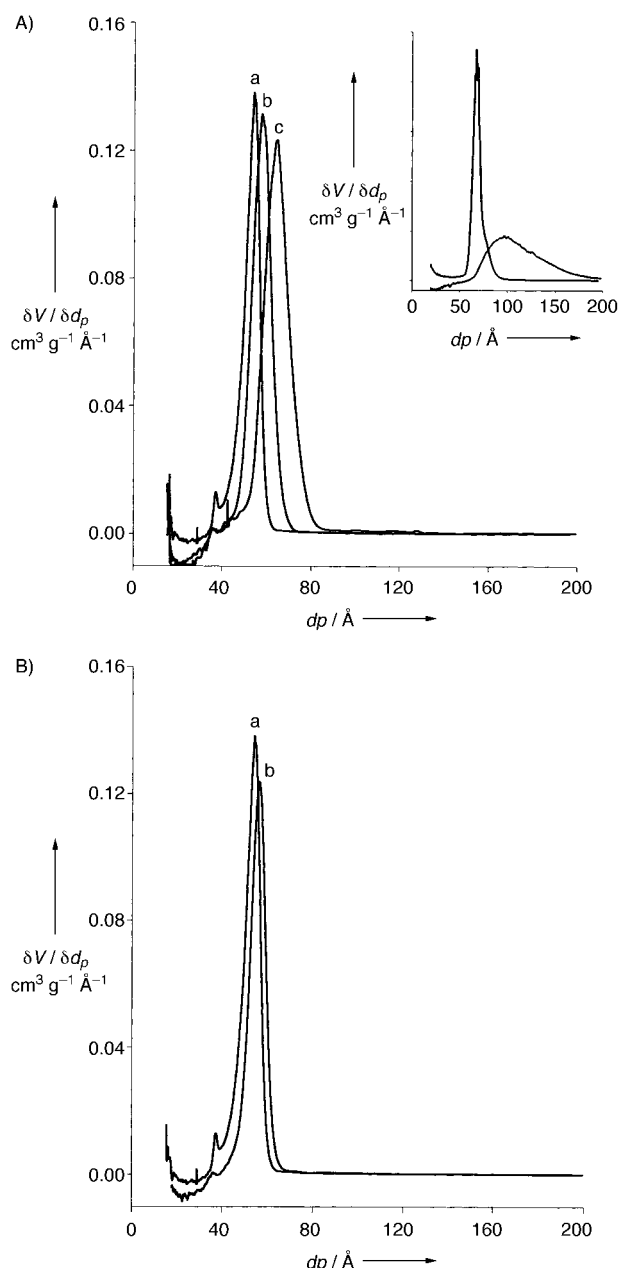


Figure 6. BJH pore diameter distributions calculated from the desorption branch of the isotherm for A) ZSM-5-coated MesoAS treated in boiling water at 100 °C: a) before and b) after treatment for 48 h and c) for 120 h (inset: the parent MesoAS sample treated in boiling water at 100 °C: a) before and b) after treatment for 48 h); and B) ZSM-5-coated MesoAS after steaming with 20% in N₂ at 800 °C: a) before and b) after steaming for 24 h.

still uniform. This indicates that the coated sample is much more hydrothermally stable than the conventional MesoAS sample. Furthermore, the coated sample was also steamed with 20% water vapor in N₂ at 800 °C for 24 h (Figure 6B). No essential change in the pore size distribution after steaming for 24 h indicates that the coated sample is hydrothermally ultrastable. We have performed a blank experiment in which the parent MesoAS was suspended in glycerol at 130 °C for 24 h. This treatment did not affect the specific surface area and pore diameter. This sample, however, did not show any improvement in hydrothermal stability compared to the

parent MesoAS sample. The remarkable hydrothermal stability observed here involves therefore the zeolite seeds coated on the mesopore surface, which act to heal defect sites in the MesoAS framework. This is likely because the 2.8 nm sized ZSM-5 seeds templated by tetrapropylammonium (TPA) ions could electrostatically interact with tetrahedral Al sites in the silica framework and as consequence of this interaction, migrate inside the mesopore channels. It is indeed significant that any attempt at coating mesostructured silica with zeolite clusters in similar preparations failed. It is also apparent that this electrostatic interaction, which provides enough mobility to the zeolite nanoparticles for their initial migration within the mesopores, does not leave these nanoparticles with sufficient mobility for their sintering during crystallization. Calcination of these materials led to grafting nanoclustered ZSM-5 particles on the mesopore surface by the condensation reaction of silanol groups at the interface. Such a coating procedure reduces the concentration of silanols, as confirmed by the ²⁹Si MAS NMR results reported in Figure 5. Consequently, the high hydrothermal stability of the coated samples should be associated with this lowered silanol surface concentration since several treatments known to decrease the silanol concentration of MMS have been shown to improve their thermal and hydrothermal stability.^[4] Finally, the strong acidity combined with an ultrastable, well-ordered uniform mesopore structure opens up new opportunities in the use of these coated materials as catalysts. These results also illustrate the potential importance of zeolite seeds as precursors for the design of this new class of materials. Indeed, our methodology is not limited to the coating by ZSM-5 seeds, since primary units with diameters of 2.8 nm for MFI/MEL structures, 2.6 nm for zeolite beta, 1.5 nm for ZSM-12, and 1.6 nm for zeolite sodalite have been reported.^[13, 14] They can potentially be used to prepare a large variety of zeolite-coated mesoporous molecular sieves.

Experimental Section

Synthesis: The synthesis of zeolite-coated mesoporous materials involves two steps: the first step consists of the preparation of the mesoporous precursor and the desired clear zeolite gel; the second step is the coating of zeolite nanocrystals on the MMS surface using the diluted clear zeolite gel. In the first step: 1) An amorphous mesoporous aluminosilicate precursor was synthesized from sodium silicate (28.7% SiO₂, 8.9% Na₂O) and sodium aluminate (46.78% Al₂O₃, 28.43% Na₂O) solutions as silicon and aluminum sources, respectively, using a poly(alkylene oxide) block copolymer HO(CH₂CH₂O)₂₀(CH₂CH(CH₃)O)₇₀(CH₂CH(CH₃)O)₂₀H (Pluronic, P123 BASF) surfactant and sulfuric acid (98%). 2) Clear ZSM-5 gel solutions with desired chemical composition were synthesized from tetraethylorthosilicate (TEOS) and sodium aluminate as silicon and aluminum sources, respectively, and tetrapropylammonium hydroxide (TPAOH) as the zeolite template. In a typical ZSM-5 gel synthesis (atomic Si/Al = 10/1), a 20% aqueous solution of TPAOH (35 g) was added to TEOS (19.5 g). To the resulting clear solution, a solution of sodium aluminate (1.08 g; 46.78% Al₂O₃, 28.43% Na₂O) in distilled water (25 g) was added. The resulting clear solution was stirred for 24 h at room temperature to form protozeolitic species (known as zeolite seeds) and was finally diluted by distilled water to a volume of 600 mL.

In the second step, 20 g of the calcined mesoporous precursor was contacted with the diluted ZSM-5 gel (600 mL) prepared above under vigorous stirring at room temperature for 1 h. The solid sample was filtered, washed with distilled water, dried at 80 °C. The resulting solid was subsequently suspended in glycerol (50 mL) and the mixture was then

transferred into a Teflon-lined autoclave and heated at 130 °C for 24 h. Glycerol was used as the medium for crystallization because due to the low solubility of silica in this medium, the framework was better retained during crystallization. Finally the solid product was filtered, washed with distilled water, dried at 80 °C, and calcined at 550 °C.

Characterization: Nitrogen adsorption/desorption isotherms at −196 °C were established by using an Omnisorp-100 apparatus. The specific surface area, S_{BET} , was determined from the linear part of the BET equation ($P/P_0 = 0.05 - 0.15$). The mesopore size distribution was calculated by using the desorption branch of the N_2 adsorption/desorption isotherms and the BJH formula. The mesopore surface area S_{BJH} and the mesopore volume V_{BJH} were obtained from the pore size distribution curves. The average mesopore diameter, D_{BJH} , was calculated as $4V_{\text{BJH}}/S_{\text{BJH}}$. Although its accuracy is limited, the BJH method, which is still universally utilized in the literature on mesoporous molecular sieves, yields results that may easily be compared with the current literature. High-resolution TEM images were obtained on a JEOL 200 CX transmission electron microscope operated at 120 kV. The samples for the TEM images were prepared by dispersing the fine powders of the products through a slurry in ethanol onto holey carbon copper grids. Solid-state ^{27}Al and ^{29}Si MAS NMR spectra were recorded at room temperature using a Bruker ASX 300 spectrometer.

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Diffusion-Limited, Aggregation-Based, Mesoscopic Assembly of Roughened Core–Shell Bimetallic Nanoparticles into Fractal Networks at the Air–Water Interface**

Yongdong Jin and Shaojun Dong*

The collective electronic, optical, and magnetic properties of organized assemblies of size-monodisperse nanocrystals are increasingly the subjects of investigation.^[1] Control over the spatial arrangement of these building blocks often leads to new materials with chemical, mechanical, optical, or electronic properties distinctly different from those of their component parts.^[2] Recently, metallic fractal clusters have sparked much interest because the localization of dynamical excitations in these fractal objects is a universal property which plays important roles in many physical processes.^[3] In particular, the localization of resonant dipolar eigenmodes can lead to a dramatic enhancement of many optical effects in fractals.^[3] For example, strongly fluctuating local fields in metallic fractal clusters can significantly exceed the external field and brings about a large enhancement of Raman scattering from the fractals.^[4] Highly localized, laser-excited optical modes of silver colloid fractal clusters have been observed by photon scanning tunneling microscopy, and the results verify the main concepts of the resonant optical theory developed for fractal objects.^[3] The localization of optical excitations and selective photomodification were also studied experimentally in fractal aggregates of silver colloidal nanoparticles.^[5] These results prelude promising interesting applications, especially towards future nano-optics.^[5, 6] Therefore, the synthesis of metallic fractal clusters is worthwhile for more detailed theoretical and technological studies.

In contrast to the wealth of recent theoretical work, experimental studies that can test the validity and applicability of modern theories have been rather sparse. In those studies performed, metallic fractal clusters were prepared from spherical colloidal particles by the addition of an adsorbate as a promoter (such as phthalazine,^[3, 7] pyridine,^[8] or gelatin,^[5]) to the solution. Strictly speaking, these aggregates are three-dimensional in solution. However, they collapse upon drying to form nearly flat, two-dimensional (2D) structures. Indeed, it is quite likely that deposition and evaporation of the colloid onto the grid lead to additional aggregation. Herein, we report on a genuine aggregation-based strategy to prepare mesoscopic, two-dimensional fractal aggregates (even thin films) of bare (without adsorbate) silver/gold roughened core–shell nanoparticles by diffusion-limited aggregation (DLA) at the air–water interface by

[*] Prof. S. Dong, Dr. Y. Jin
State Key Laboratory of Electroanalytical Chemistry
Changchun Institute of Applied Chemistry
Chinese Academy of Sciences
Changchun 130022, Jilin (P.R. China)
Fax: (+86) 0431-5689711
E-mail: dongsj@ns.ciac.jl.cn.

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thermoaccelerated electroless plating. We also demonstrate that control over the concentration of the plating solution can not only be used to fine-tune the resulting fractal patterns, but can also drastically affect the crystal growth of the particles.

The Ag nanoparticles prepared by trisodium citrate reduction of AgNO_3 ^[9] generate faceted particles with a diameter of about 50 nm, as confirmed by transmission electron microscopy (TEM, Figure 1A). We used those preformed Ag nanoparticles as seeds to prepare colloidal silver/gold core-shell bimetallic nanoparticles by electroless plating^[10, 11] and

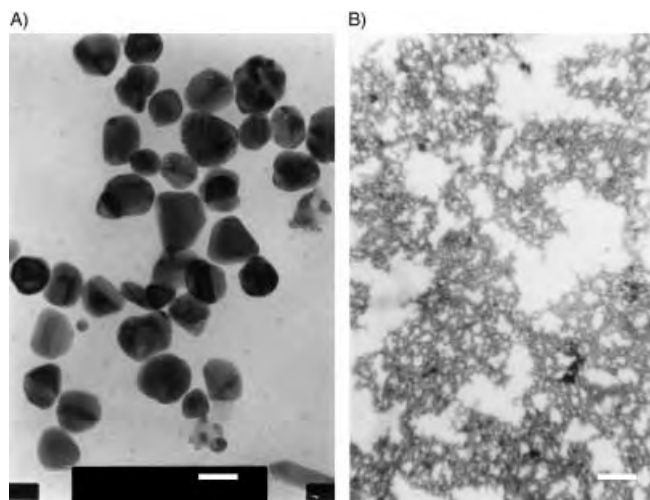


Figure 1. A) TEM image of trisodium citrate prepared Ag nanoparticles showing the size and facet of particles; scale bar = 50 nm. B) Optical microscope image of as-prepared mesoscopic fractal aggregates of Ag/Au core-shell composite nanoparticles. Note the resemblance of the dendritic outline to the modeled results of DLA of metal particles;^[12, 13] scale bar = 0.1 mm.

demonstrated that the shapes of the resulting particles could be conveniently varied from a nearly spherical morphology to a roughened one by controlling the plating temperature. We also found that the heating time is crucial for preparing roughened colloidal particles. Overheating causes the resulting roughened colloidal particles to float up and be liberated at the air-water interface, a process which results in the formation of fractal aggregates. In the preparation of sample 1, the solution obtained on addition of plating solution ($\text{HAuCl}_4/\text{NH}_2\text{OH}$) exhibited a dramatic color change from greenish yellow, which is typical for uncoated Ag sols, to blue. After boiling the solution for about 5 min, some small black dots emerged which could be seen at the air-water interface by the naked eye. The dots grew quickly and exhibited fractal-like patterns on the millimeter to centimeter scale within a few minutes. No precipitate formed during the procedure. The optical photograph of these fractal aggregates (Figure 1B) shows they are open-structured and in good agreement with the modeled results of diffusion-limited aggregation of metal particles.^[12, 13] The composite nanoparticle aggregates exhibit unique collective optical properties, such as being blue colored with a gold reflectance, which are indicative of the existence of hundreds and thousands of linked Au-coated Ag nanoparticles.

We further investigated the fine structures of the fractal aggregates directly by TEM. To our surprise the nanoparticles slightly agglutinate to yield networks (Figure 2A) and link

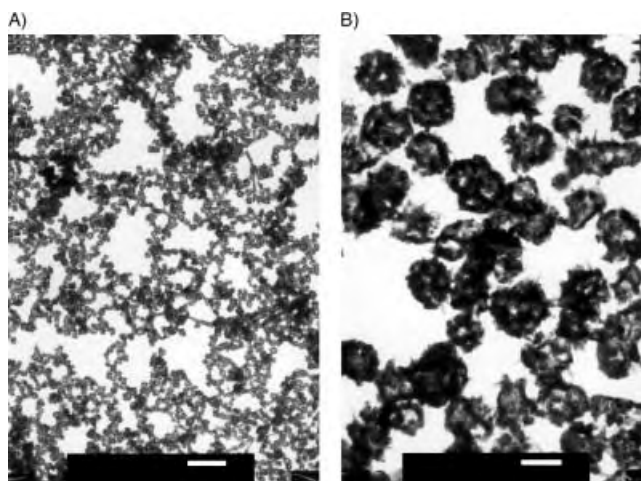


Figure 2. A) TEM image of sample 1 showing the fractal network of linked and still well-dispersed nanoparticles; scale bar = 500 nm. B) A high magnification TEM image of (A). Note the core-shell structure and roughened morphology of the nanoparticles. These composite nanoparticles stick together through the whiskers of particles; scale bar = 100 nm.

together through “junctions” to form a well-defined, two-dimensional porous structure. Aggregation does not produce coalescence into larger particles, but instead produces assemblies of nanoparticle monomers. No three-dimensional aggregation occurs. The morphology is characterized by their tenuous, chainlike structure, and is scale invariant, that is, fractal.^[8, 13] An enlarged TEM image clearly showed that the composite nanoparticles are still well dispersed and consist of very uniform diameter crystalline cores (typically about 50 nm in diameter) surrounded by a heterogeneous roughened (whiskerlike) coating (Figure 2B). Indeed, the core-shell nanoparticles stick together through the whiskers of the particles. No whisker growth was evident in a control experiment without heating. This result suggests that there is a thermo-induced preferential direction of growth of Au on the facets of Ag nanoparticles. This growth of the whiskers occurs as a result of differences in the curvature-dependent local chemical potentials.^[14] We elucidated the composition of the core and whiskerlike shell by using X-ray photoelectron spectra (XPS) analysis of self-assembled monolayers on glass slides modified with 3-aminopropyltrimethoxysilane (APTMS) before and after electroless Au plating (Figure 3). These experiments, in combination with TEM image analysis,^[11] revealed that the prepared Ag/Au nanoparticles had a core-shell structure, and confirmed that the particles consist of an Ag core and an Au shell enriched with Ag.^[11]

The fractal patterns of the nanocrystal aggregates can be fine-tuned by changing the concentration of the plating solution. At low HAuCl_4 concentrations (sample 2) there are more open spaces in the well-ramified pattern and whisker-linked nanoparticles align almost one-by-one (Figure 4A). More interestingly we also observed a seed particle

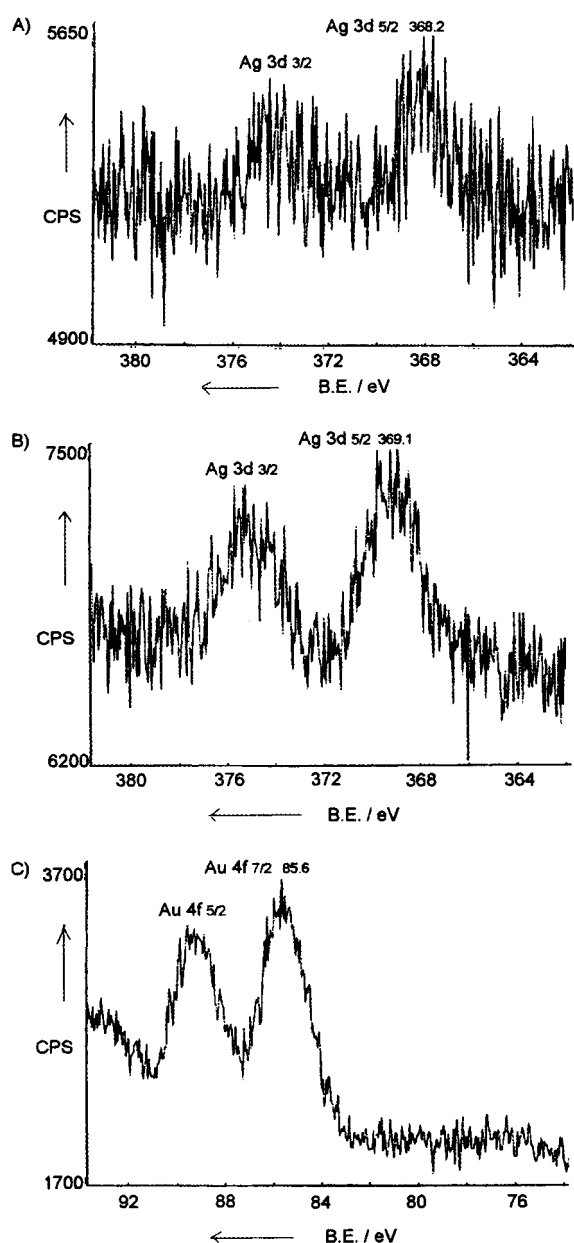


Figure 3. XPS (ESCLAB MKII, using Mg as the exciting source) analysis of Ag 3d orbitals of the Ag nanoparticles prepared by trisodium citrate reduction (A), the Ag 3d orbitals (B), and Au 4f orbitals (C) of as-prepared Ag/Au core-shell roughened nanoparticles. B.E. = binding energy, CPS = counts per second.

(blackest dot in Figure 4B) in the selected image area, which is typically characteristic of a DLA model.^[12] At higher HAuCl_4 concentrations (sample 3) the particles are linked relatively compactly and there are less crevices in the networks (Figure 5A), which fit better to the Eden model^[12, 13]—a lattice model in which particles are added one at a time to random sites adjacent to occupied sites. The TEM images show that increasing the concentration of HAuCl_4 changes the fractal patterns of the resulting aggregates from a DLA model to an Eden-like model. It is also noteworthy that the as-prepared 2D fractal aggregates are robust and flexible, which can be confirmed by the presence of some small particle loops in the TEM images.

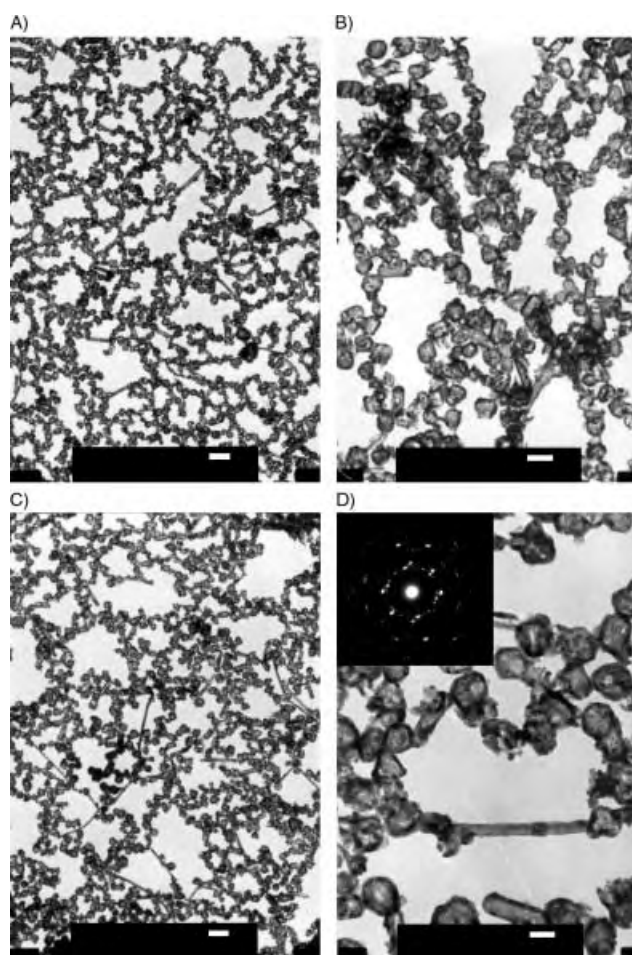


Figure 4. A) A typical TEM image of sample 2. The composite particles aligned almost one-by-one and well ramified; scale bar = 200 nm. B) A high-magnification TEM image of (A) showing a seed particle (black dot) in the selected area and its following DLA growth traces; scale bar = 100 nm. C) Another typical TEM image of sample 2, which explicitly shows the presence of some nanorods and nanowires; scale bar = 200 nm. D) A high-magnification TEM image of a resulting nanowire and the corresponding electron diffraction pattern (inset); scale bar = 50 nm.

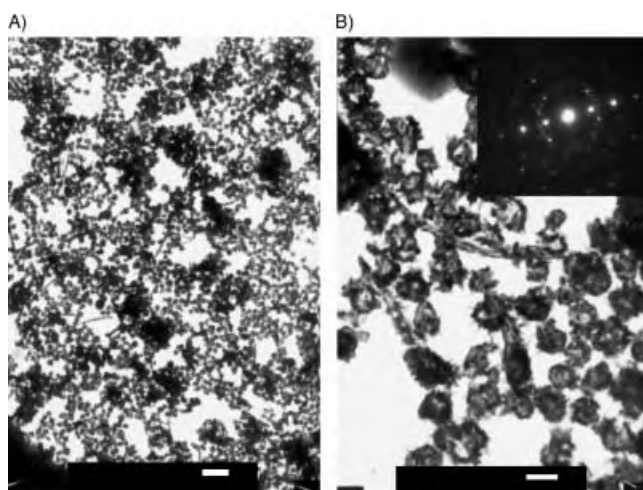


Figure 5. A) A typical TEM image of sample 3 showing the size and shape distribution of single crystals growing in a nanoconfined environment among the relatively compact particle network; scale bar = 500 nm. B) A high-magnification TEM image of a resulting single crystal in (B) and the corresponding electron diffraction pattern (inset); scale bar = 100 nm.

The TEM images also showed that a variation of the HAuCl_4 concentration affects the crystal growth of the particles, as well as changing the fractal pattern of resulting aggregates. When the HAuCl_4 concentration is increased, the shell thickness increases and the whiskers grow faster and longer. Interestingly, many large, square and triangular single crystals begin to grow and scatter evenly among the networks, as evident in Figure 5A and confirmed by the corresponding electron diffraction pattern (Figure 5B). We were able to determine the three-dimensional shapes of the particles by tilting the samples in the TEM experiment. The particles with square outlines were found to be cubic, while those with triangular outlines were tetrahedral. No large single crystals grow in the nanoconfined environment at low HAuCl_4 concentrations, but many nanorods and nanowires grow instead. Figure 4C shows a typical image of the resulting nanorods and nanowires. It clearly shows that the remarkably uniform diameters of the nanowires are on the order of about 50 nm (dictated almost by the diameter of the Ag particles) and the length is on the order of about 0.5–1 μm . Furthermore, the highly crystalline nature of the resulting nanowires was confirmed by selected-area electron diffraction measurements on these nanowires (Figure 4D). The diffraction spots/rings reveal a hexagonal diffraction spot pattern, which indicates that the Au nanowires prepared by surface catalysis of the Ag nanoparticles are almost single crystals growing along the [111] direction. Incidentally, the growth behavior of the resulting nanowires is very similar to that seen in the catalytic synthesis of nanowires by laser ablation.^[15]

An experimental model to shed further light on the growth process of these fractal aggregates is shown in Figure 6. When the reaction solution is heated, thermo-induced selective growth of Au on the surface of Ag nanoparticles results in the rapid growth of whiskers. When the whiskers have grown long enough, the resulting global dendrites float up and are liberated at the air–water interface as “random walkers”.^[13] They wander freely and quickly until they collide and irreversibly stick together,^[16] by a subsequent deposition step, to become part of the cluster. The initial liberated particle acts as a seed particle during this cluster aggregation. The exposed ends of the clusters grow more rapidly than the interior since the “random walkers” are captured before they reach the interior. Thus, the resulting cluster has a tenuous treelike and open structure because holes are formed and not filled up.^[13] Following cluster aggregation, the cluster–cluster aggregation proceeds^[13] to produce more open and fluffy structures. As a result, the aggregates grow and finally reach millimeter to centimeter scales at the air–water interface.

It is well known that DLA is an idealization of the process by which matter irreversibly combines to form dust, soot, dendrites, and other random objects when the rate-limiting step is the diffusion of matter to the aggregate. The growth of a DLA cluster is determined by the set of growth probabilities $\{P_i\}$, where P_i is the next unit to be added to the cluster.^[17] The simplicity of the experiments described here represents a good experiment model and is of fundamental and technological interest to gain insight into the nature of DLA and controlled fractal growth.

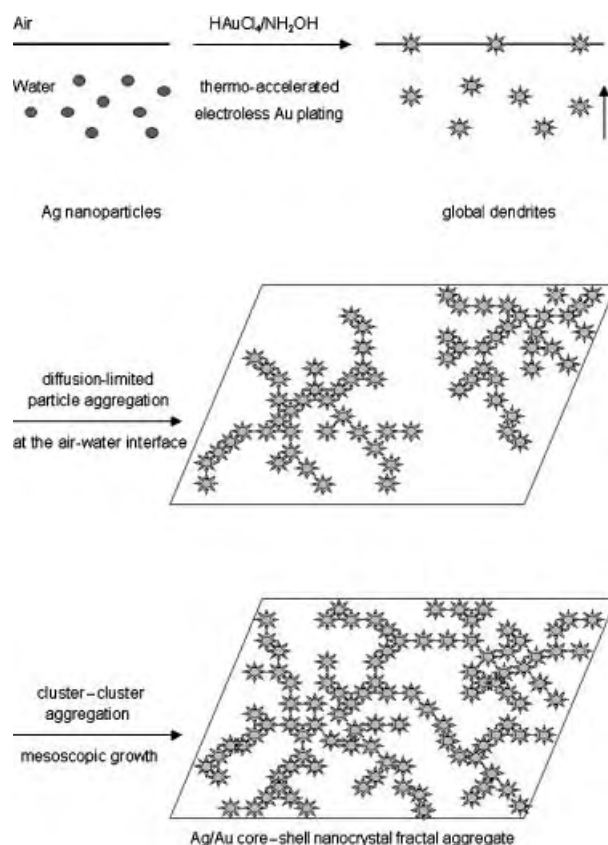


Figure 6. Schematic representation of the growth and assembly process of silver/gold roughened core-shell nanoparticles into mesoscopic fractal networks at the air–water interface.

It is important to note that the as-prepared fractal aggregates consist of hundreds and thousands of structurally well-defined Ag/Au core–shell nanoparticles, which may exhibit unique mesoscopic electrical and optical properties^[3–6] that depend sensitively on both the size and fractal dimensionality. The method described here should be useful, not only for testing theories of fractal growth, but also for enriching synthetic methods of nanomaterials with controlled properties. Importantly, the ease of solution-phase synthesis in combination with the ability to control the long-range assembly of the composite nanoparticles into continuous fractal-defined structures make this artificial “macromolecules” architecture—silver nanoparticles (artificial atoms) linked together by nanoscale gold whiskers (bonds)—a further step toward artificial solids made of large arrays of linked dots.^[18] Very recently, we have also found, by mild modification of the method described herein, that the fractal aggregates can gradually grow and finally fill the whole surface of the container used, thus proving that it is possible to scale-up this technology for the facile preparation of quasi-two dimensional, structurally well-defined porous fractal thin films of composite roughened nanoparticles with controlled sizes. This possibility will hold great promise for potential fundamental and technological applications.^[3–6, 18]

Experimental Section

Analytical grade $\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$, trisodium citrate, hydroxylamine hydrochloride, and AgNO_3 were all obtained from Aldrich and used without

further purification. All glassware used in the following procedures were cleaned in a bath of freshly prepared 3:1 HCl:HNO₃ (aqua regia) and rinsed thoroughly in milli-Q grade water prior to use. The Ag nanoparticles were prepared by sodium citrate reduction of AgNO₃.^[9] AgNO₃ (18 mg) was dissolved in H₂O (100 mL) and brought to reflux. A solution of 1% trisodium citrate (2 mL) was added and the solution was kept at reflux for about 1 h. The final volume was adjusted to 500 mL. The Ag sols prepared were greenish yellow. The Ag plasmon absorbance maxima was at approximately 440 nm.

In a typical synthesis, as-prepared Ag sols (5 mL) was diluted with water (5 mL), then a freshly prepared plating solution of 0.02 M NH₂OH (0.10 mL) and 0.1% HAuCl₄ (0.25 mL) was added with stirring. The solution was then heated at reflux for about 10 min before cooling it down to room temperature. It was now ready for TEM sample preparation (sample 1). Samples 2 and 3 were prepared by adding 0.10 and 1.0 mL of a 0.1% solution of HAuCl₄ to the aliquot Ag sols, respectively, and then following the same procedure as for sample 1. The initial ratios of the concentration of the HAuCl₄ solution were 2.5:1:10 for samples 1, 2, and 3, respectively.

Samples for TEM were prepared by placing a drop of solution (for sol) on or transferring as-prepared thin film to a carbon-coated copper grid. Samples were examined by using a JEOL 2010 transmission electron microscopy operated at 200 kV. Analysis of the X-ray photoelectron spectra (XPS) was performed on a ESCLAB MKII using Mg as the exciting source.

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The First Water-Soluble Copper(I) Calix[6]arene Complex Presenting a Hydrophobic Ligand Binding Pocket: A Remarkable Model for Active Sites in Metalloenzymes**

Yannick Rondelez, Gildas Bertho, and Olivia Reinaud*

Because of the unique properties of water, the synthesis of biomimetic complexes that are soluble and stable under physiological conditions is an attractive goal. Paradoxically, most metalloenzyme models have been developed in organic solvents.^[1] The first reason is that the ligands used to mimic the biological active site often lead to water-insoluble complexes, and their solubilization through synthetic procedures is not an easy task. For instance, tris(pyrazolyl)borate, which is the basis for countless biomimetic complexes,^[2] is sensitive to hydrolysis, and hydrophilic derivatives would not survive in aqueous solvent.^[3] The second reason is that biologically relevant species are often reactive to water and must be protected and/or stabilized. In the specific case of copper, few water-soluble cuprous complexes have been described,^[3, 4] and to the best of our knowledge none of them can be considered biomimetic. Indeed, it is well known that Cu^I centers are thermodynamically unstable in water and disproportionate in the absence of an appropriate coordinating environment. Another major difficulty stems from the fact that metalloenzyme model complexes must present a vacant or a labile site on the metal center to allow the coordination and/or activation of a guest.

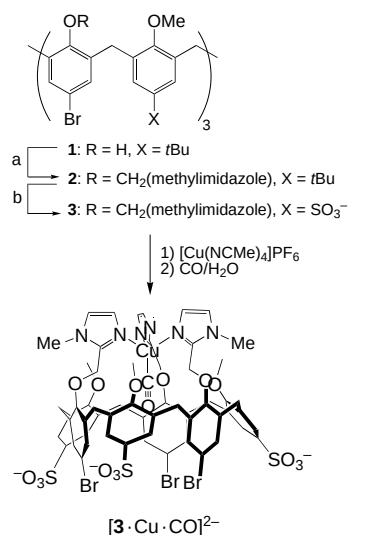
In the course of modeling type 2 active sites of copper enzymes, we have been interested in developing a supra-molecular system that can stabilize a copper(I) center within a biomimetic environment.^[5–7] We have now extended our previous work to demonstrate a possible route to transform the calix[6]arene derivatives soluble in organic solvents into compounds soluble in water. Here, we describe the synthesis of the first water-soluble biomimetic cuprous complex.

The selectively functionalized calix[6]arene derivative **1**^[8] was first *O*-alkylated with three imidazole arms to yield compound **2** (Scheme 1).^[6] The next step consisted of the *ipso* sulfonation of the three anisole rings by treating **2** with concentrated sulfuric acid. The resulting triacid **3**·H₃ was neutralized with sodium hydroxide, giving rise to the trisodium salt **3**·Na₃. This new ligand is highly soluble in water and, to a lesser extent, in methanol, ethanol, and 2-propanol.

[*] Dr. O. Reinaud, Y. Rondelez, G. Bertho
Laboratoire de Chimie et Biochimie Pharmacologiques
et Toxicologiques
CNRS UMR 8601, Université René Descartes
45 rue des Saints-Pères, 75270 Paris Cedex 06 (France)
Fax: (+33) 1-42-86-83-87
E-mail: reinaud@biomedicale.univ-paris5.fr

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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. Synthesis of the biomimetic water-soluble cuprous complex [3·Cu·CO]²⁻. a) 2-chloromethyl-1-methyl-1*H*-imidazole, NaH, THF, 55 % yield; b) conc. H₂SO₄; aq. NaOH, 72 % yield.

Its ¹H NMR spectrum attests to a very flexible molecule displaying structural interconversion (Figure 1 a).

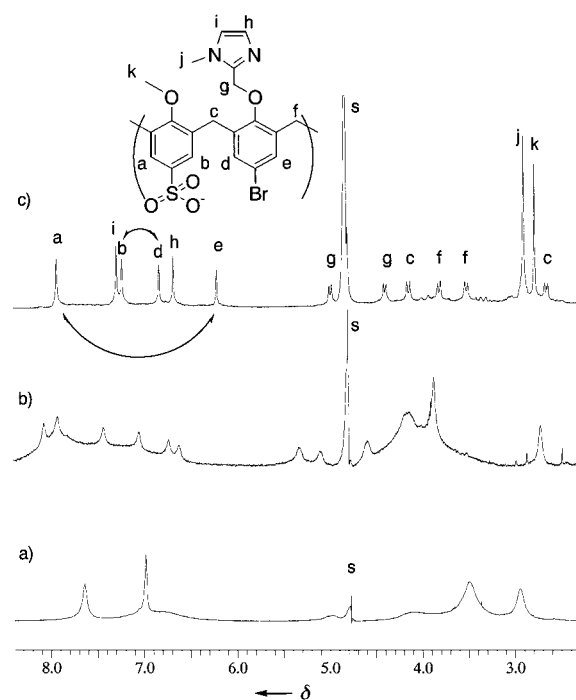


Figure 1. 500 MHz ¹H NMR spectra in D₂O: a) ligand [3]·Na₃ at 300 K, b) complex [3·Cu]·Na₂ at 320 K, and c) complex [3·Cu·CO]·Na₂ at 300 K. Concentrations are about 10⁻³ mol L⁻¹. The signal of the undeuterated solvent was irradiated and the remaining peak is labeled "s". Important NOE effects are indicated by arrows. Labeling of the protons is indicated on the structure.

Complex [3·Cu⁺]·Na₂ was obtained by mixing stoichiometrically ligand [3]·Na₃ and [Cu(NCMe)₄]PF₆ in ethanol. This new complex, which spontaneously precipitated out of the ethanolic solution, is readily soluble in water. Like its organic-solvent soluble analogue,^[5] complex [3·Cu⁺]·Na₂ is

resistant to air autoxidation since no paramagnetic signal was detected by EPR after the solution was exposed to air for one day. The ¹H NMR spectrum in water shows very broad signals, on the top of which a set of well-defined resonances is observed (Figure 1 b). The relative importance of the latter increased upon raising the temperature (from 4 to 80 °C) or upon dilution. This suggests that the broad resonances are due to an ill-defined aggregated state. In contrast, the set of relatively narrow peaks agrees with a C₃-symmetrical monomeric species, in which the cuprous ion is bound in a trigonal fashion to the three imidazole moieties of the ligand.^[9] The complex reacts with carbon monoxide in either water or methanol. The subsequent solution IR spectrum, displaying an absorption at 2075 cm⁻¹, confirms the presence of CO as a fourth ligand.^[10] The new adduct displays a distinct and better resolved ¹H NMR spectrum (Figure 1 c). The conserved C₃ symmetry indicates that the three imidazolyl groups are still bound to the metal ion. Each proton resonance was assigned based on COSY, NOESY, HMBC, and HSQC experiments, and a proposed structure is displayed in Scheme 1.

The coordinating imidazole moieties wrap the cuprous ion in a helical fashion. As a result, the complex exists as two C₃-symmetrical enantiomers. The helicity is transmitted to the arene rings as shown by the large diastereotopic splitting of their ¹H resonances (Δδ = 0.70 (H_a,H_b) and 0.62 (H_d,H_e), see Figure 1 c). NOESY correlations were observed between each pair of aromatic protons, thereby substantiating a *cone* conformation for the calixarene structure.^[11] The signals of the deshielded phenoxy protons correspond to the anisole moieties which indicates that the hydrophilic sulfonate groups are pointing outward from the cavity, toward the solvent.^[12, 13] Finally, no exchange peaks between the diastereoisomeric protons were observed in the 2D experiments (NOESY and ROESY, τ_m = 200 to 500 ms). Neither were the proton resonances broadened upon heating up to 350 K. This indicates that the exchange rate between the two helical enantiomeric conformations of [3·Cu·CO]·Na₂ is particularly slow. At a high temperature, however, slow release of CO was observed.

This novel water-soluble calixarene-based system displays some remarkable features. 1) It allows the formation of a N₃Cu^I complex with a fourth binding site that is accessible for an exogenous ligand with a strong affinity for the metal ion such as CO. 2) In spite of this labile site and owing to its protection by the calixarene structure, the cuprous complex is resistant to disproportionation and to air autoxidation. It also shows that the coordinating environment provided by three imidazole moieties which mimics the tris(histidine) binding site often encountered among enzymes is indeed capable of stabilizing a cuprous center in water. 3) The calix[6]arene adopts a relatively rigid *cone* structure that encloses a well-defined hydrophobic cavity. This is unusual for sulfonated calix[6]arenes. Indeed, the hexasulfonated calix[6]arene derivatives have been described as highly flexible molecules with a preferred 1,2,3-*alternate* conformation.^[14] In our system, the rigidity of the host results from the binding of a metal cation and the *cone* conformation is favored by the relatively smaller electrostatic repulsion on the large rim bearing only three sulfonates.

The highly restricted mobility of the helical arrangement of the imidazolyl groups is more surprising. A tentative explanation can be proposed. First, the complex displays some large hydrophobic domains and solvation effects may increase the interconversion energy barrier. Second, electrostatic repulsion between the anionic sulfonates together with some stabilizing hydrophobic interactions between the three “in” *p*-bromophenyl groups may freeze the movements of the molecule. Indeed, we have already shown that, in these systems, the structural information is very efficiently conveyed from one side of the molecule to the other.^[5] As a consequence, restricted mobility of the large rim may be responsible for the freezing of the imidazolyl helix of at the narrow rim.

This work demonstrates the successful transposition of an organic-solvent soluble biomimetic system into aqueous solvent. Careful functionalization of the calixarene-based ligand has allowed the retention of the most important properties of the complex: the stabilization of the cuprous center despite the presence of a free valence, the protection of the metal site in the concave area of a hydrophobic cavity, and the host behavior of the complex toward a small coordinating guest. This novel supramolecular system reproduces not only the first coordination sphere encountered in many enzymes and the frequently hydrophobic microenvironment of the active site, but also the aqueous macroenvironment of a physiological medium. We are currently exploring its behavior as a selective hydrophobic receptor^[15] for a variety of guest molecules in water. Future developments may also lead to “green” catalysts.^[16]

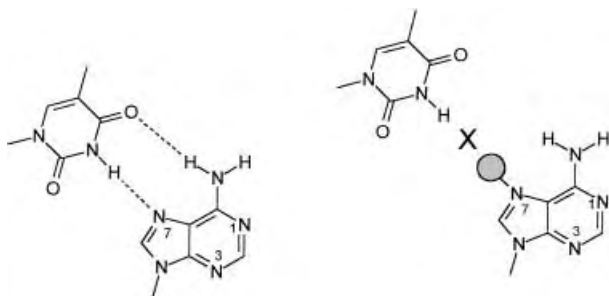
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- [12] The $\Delta\delta$ shifts for H_a vs H_d and H_b vs H_e are 1.09 and 1.01, respectively. This is much higher than the shift by ca. 0.5 expected for a simple electronic effect due to the bromo and sulfonato substituents. For *para*-substituted toluenes the *ortho* protons (relative to Br or SO_3^-) have chemical shifts of $\delta = 7.35$ ($CDCl_3$) and 7.85 (D_2O), respectively. Therefore, we can assume that the largest $\Delta\delta$ observed for the $CuCO$ complex reflects conformational effects with H_{Ar} being in either *in* or *out* position relative to the aromatic walls of the calixarene cone (see ref. [11]).
- [13] Among the *tert*-butylated organic-solvent soluble analogues, the complexes bearing three *O*-methyl groups were shown to include one of their *t*Bu moieties into the calixarene pocket which lead to a dissymmetric conformation. This move is obviously disfavored by the replacement of *t*Bu groups by sulfonates. Hence, the overall properties the water-soluble $CuCO$ complex are more reminiscent of those reported for the organic-solvent soluble parent compound bearing three *O*-ethyl substituents (see ref. [5b]). However, the relative *alternate* position of the phenoxy walls is now reversed and corresponds to that depicted for the Cu^I -nitrilo complex in ref. [5a]. This may be due to the hydrophobic effect, which pushes the methoxy groups toward the cavity away from water.
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Self-Complementary Metal Complexes Containing a DNA Base Pair**

Clayton Price, Benjamin R. Horrocks, Annabelle Mayeux, Mark R. J. Elsegood, William Clegg, and Andrew Houlton*

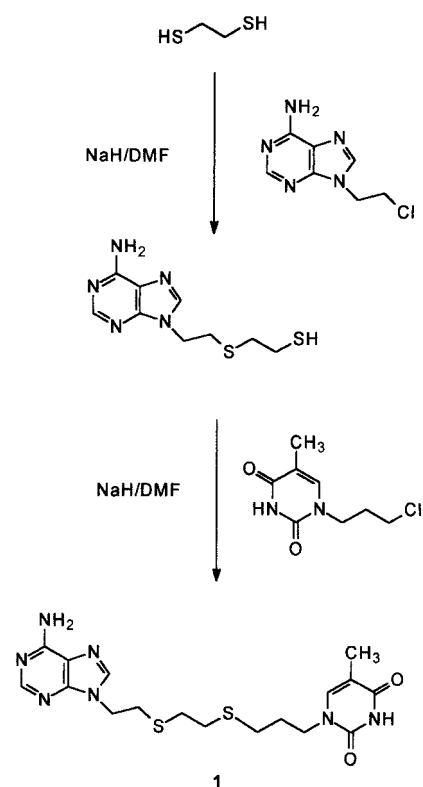
DNA-type interactions such as hydrogen bonding and aromatic stacking can be used to control the molecular assembly of synthetic compounds in solution and in the solid state.^[1] As nucleobases can bind metal ions, base-pairing interactions can be used directly in their complexes.^[2] However, in some instances prediction of the resulting assembly is difficult because certain key hydrogen-bond acceptor sites are also preferred for metal-ion binding. This is especially true for the adenine–thymine (AT) pair, in which there are numerous possibilities for interactions which involve two hydrogen bonds (for example, $A_{WC} \cdots T$, $A_H \cdots T$, $A_H \cdots A_H$, $A_{WC} \cdots A_{WC}$, $A_{WC} \cdots A_H$, $T \cdots T$, etc.; where WC and H denote Watson–Crick and Hoogsteen faces). The thermodynamically favored arrangement is the Hoogsteen AT pattern, which involves A–N7^[3] (Scheme 1, left). However, since this is also the



Scheme 1.

preferred site for metal-ion binding (right), this pairing mode is often unavailable. Recently, we have been developing the chemistry of chelate-tethered nucleobase strands that can give atypical coordination at the nucleobase.^[4] In particular we were able to rationally synthesize A–N3-bound complexes. Such compounds should be capable of undergoing a Hoogsteen interaction with thymine and thus assemble in a predictable manner. Here we demonstrate this with the synthesis of a bis-nucleobase ligand strand **1** containing A and T as substituents.^[5, 6] The dithioether **1** reacts with Pd^{II} and Pt^{II} to give cationic A–N3-bonded complexes **2** and **3**. Furthermore, the complexes assemble in the solid state in the predicted manner.

The synthesis of the dithioether ligand strand **1** is summarized in Scheme 2 and involves two successive deprotonation/



Scheme 2. Synthesis of **1**.

alkylations of 1,2-dithioethane with 9-(2-chloroethyl)adenine^[4b] and 1-(3-bromopropyl)thymine,^[6a] respectively, to give **1** in 34% yield. The compound is moderately soluble in methanol, DMSO, and DMF.

Reaction of **1** with $[PdCl_2(MeCN)_2]$ in refluxing MeCN/MeOH or $K_2[PtCl_4]$ in $H_2O/EtOH$ gives monocationic complexes $[PdCl(\mathbf{1})]^+$ (**2**) and $[PtCl(\mathbf{1})]^+$ (**3**), which were isolated as BF_4^- salts by addition of a saturated aqueous solution of $NaBF_4$. The resulting complex salts are soluble in water and DMSO. The ^1H NMR spectrum in $[D_6]DMSO$ shows marked shifts of individual signals relative to **1**. Most dramatic, perhaps, is the effect on the A–N6H₂ signal, which moves significantly downfield and the splitting of which indicates restricted rotation about the exocyclic amino group upon complexation (**1**: $\delta = 7.23$; **2**: $\delta = 8.37, 8.46$; **3**: $\delta = 8.47, 8.57$). Also apparent was the effect of slow inversion at sulfur on some signals (for example, A–H2: **1**: $\delta = 8.16$; **2**: $\delta = 8.36, 8.37$; **3**: $\delta = 8.41, 8.43$; A–H8: **1**: $\delta = 8.14$; **2**: $\delta = 8.26, 8.28$; **3**: $\delta = 8.28, 8.29$). This was also seen in the ^{195}Pt NMR spectrum of **3**, which contains two signals ($\delta = -2137, -2124$) in a 1:2 ratio. Coordination to A–N3 can also be deduced from the downfield shift for the protons on C10 (**1**: $\delta = 4.36$; **2**: $\delta = 5.00, 5.16$; **3**: $\delta = 5.07, 5.13$). This effect is characteristic for N3 binding.^[4a,c,d,f, 7] Complexation has little effect, however, on the positions of the thymine group signals (for example, T–N3H: **1**: $\delta = 11.28$; **2**: $\delta = 11.30$; **3**: $\delta = 11.29$).

Based upon these spectroscopic data and the known binding modes for adenine-only analogues^[4] of **1** it was anticipated that the dithioether group and the A–N3 site would coordinate to the metal ions. X-ray crystallography^[8] confirms this for both **2** and **3** (Figure 1), which are

[*] Dr. A. Houlton, Dr. C. Price, B. R. Horrocks, A. Mayeux, Dr. M. R. J. Elsegood, Prof. Dr. W. Clegg
Department of Chemistry, University of Newcastle upon Tyne
Newcastle upon Tyne NE1 7RU (UK)
Fax: (+44) 191-222-6829
E-mail: andrew.houlton@ncl.ac.uk

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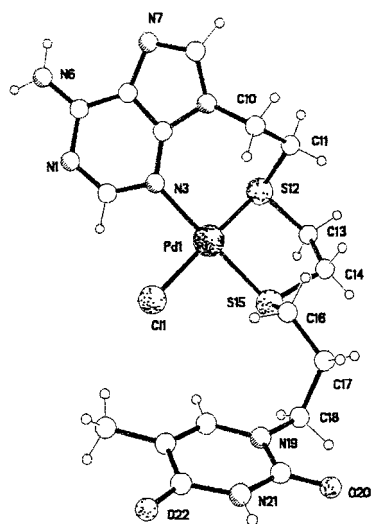


Figure 1. Molecular structure of the cation in **2**. Selected bond lengths [$\text{\AA}$]: Pd1-N3 2.051(7), Pd1-S12 2.267(2), Pd1-S15 2.261(2), Pd1-Cl1 2.315(2). The Pt complex **3** is isostructural. Pt-N3 2.058(4), Pt-S12 2.2562(12), Pt-S15 2.2583(12), Pt-Cl1 2.3225(12). The angles between the adenine and thymine planes is 67.8° (**2**) and 68.6° (**3**).

isostructural. In each complex the central metal ion has a slightly distorted square-planar geometry, and **1** acts as a tridentate ligand. The coordination forms five- and seven-membered chelate rings, and the nucleobase is inclined at an angle of 46.2° in **2** and 45.7° in **3**. The angle between the coordinated A and the pendant T is 67.8° in **2** and 68.6° in **3**. Compound **3** is a rare example of a Pt–N3 adenine complex.^[7] Interestingly, this type of binding was recently observed in the reaction of the antitumor drug *trans*-[PtCl₂{(E)-HN=C(O-Me)Me}₂] with the ribonucleotide r(ApG) in the formation of a 1,2-intrastrand adduct.^[7b]

Analysis of the molecular packing reveals the expected Hoogsteen base pairing between cations ($\text{O4}_T \cdots \text{N6}_A$ 2.940, $\text{N3}_T \cdots \text{N7}_A$ 2.886 $\text{\AA}$; Figure 2). Infinite base-paired chains are formed by translational symmetry and have a repeat distance of 14.8 $\text{\AA}$. The crystal symmetry produces antiparallel alignment of neighboring chains. Further interactions between the nucleobases involve dimers of stacked AT pairs that are slipped so as to form ATTA sequence runs with typical separations for π – π stacking (Figure 3).

In summary, controlling the metal ion nucleobase binding pattern by using a chelating group enables the synthesis of base-pairing complexes that assemble in a predictable arrangement. We are currently investigating further complexation reactions of **1** with regards to metal–ligand stoichiometry and metal ion coordination geometry. In particular it is

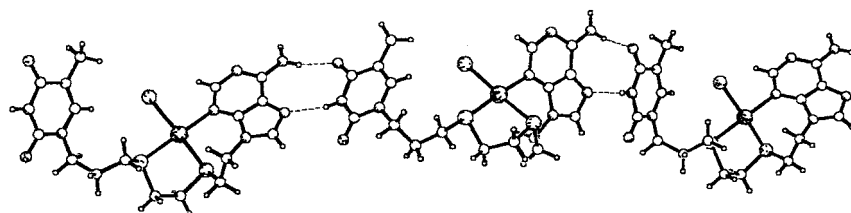


Figure 2. Hoogsteen base pairs formed between complex cations in **2**. A $\cdots$ T interplanar angle is 19° .

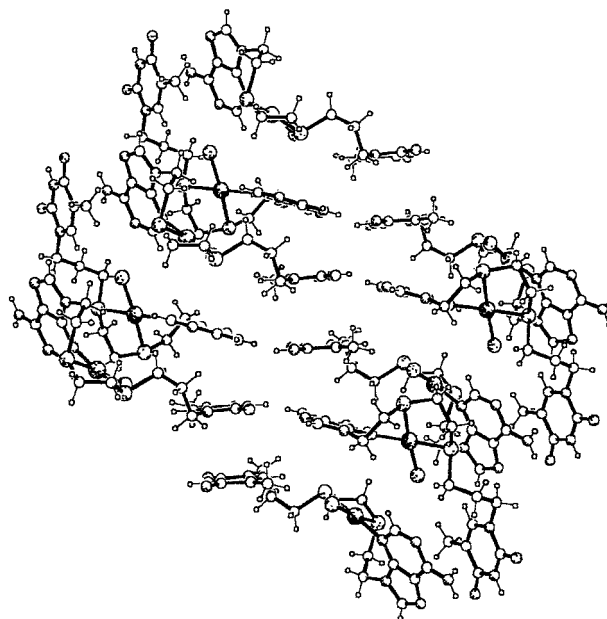


Figure 3. π – π stacking interactions between base pairs in **2** occur in ATTA sequence. Interplanar T $\cdots$ T distance about 3.394 $\text{\AA}$; interplanar angle A $\cdots$ T 19° .

envisaged that dinucleobase duplex and triplex structures can be assembled by analogy with simple bis- and trischelate complexes.

Experimental Section

1: NaH (0.12 g, 5.06 mmol) was added to a solution of 1,2-ethanedithiol (0.48 g, 0.42 mL, 5.06 mmol) in dry DMF (100 mL), and the mixture stirred until hydrogen evolution ceased. 9-(2-Chloroethyl)adenine (1.00 g, 5.06 mmol) was added and the mixture was allowed to stir. After 16 h a second equivalent of NaH was added (0.12 g, 5.06 mmol), and the mixture was again stirred until H₂ evolution ceased. A solution of 1-(3-bromopropyl)thymine (1.25 g, 5.06 mmol) in dry DMF (100 mL) was added, and the suspension was stirred for a further 16 h. The solution was filtered (Celite) and taken to dryness under reduced pressure, water (100 mL) was added, and the slurry was extracted into dichloromethane (3×300 mL). The organic extracts were dried (Na₂SO₄), and after evaporative removal of the solvent the crude product was purified by column chromatography (matrix 60 silica) with 15% EtOH in dichloromethane as eluent. Yield: 0.72 g, 34%. ¹H NMR ([D₆]DMSO, TMS): δ = 1.62 (s, 3H, Thy-CH₃), 1.85 (m, 2H, H17), 2.51 (t, 2H, H16), 2.70 (m, 4H, H13, H14), 3.04 (t, 2H, H11), 4.35 (t, 2H, H18), 4.36 (t, 2H, H10), 7.23 (brs, 2H, H6), 7.54 (s, 1H, Thy-H6), 8.14 (s, 1H, Ade-H8), 8.16 (s, 1H, Ade-H2), 11.28 (s, 1H, Thy-NH3); MS: *m/z*: 422 [*M*+H]⁺; elemental analysis (%) calcd for C₁₇H₂₃N₇O₂S₂: C 48.32, H 5.49, N 23.20; found: C 48.40, H 5.29, N 22.37.

2: To a refluxing solution of PdCl₂ (0.038 g, 0.21 mmol) in MeCN (10 mL) was added dropwise a methanolic solution (10 mL) of ligand **1** (0.088 g, 0.21 mmol), and the mixture was refluxed overnight. The cooled solution was taken to dryness under reduced pressure, and the resultant solid residue dissolved in hot water (50 mL). The mixture was filtered to remove undissolved solids and concentrated to a minimum volume in vacuo. Addition of a saturated aqueous solution of NaBF₄ precipitated **2** as a yellow solid, which was washed with water, ethanol, and diethyl ether and pump dried. Yield 0.09 g, 66%. ¹H NMR ([D₆]DMSO, TMS): δ = 1.76, 1.77 (s, 3H, Thy-CH₃), 2.15 (m, 2H, H17), 3.17 (m, 2H, H16), 3.26 (d, 1H, H13'), 3.49 (m, 2H, H14, H14'), 3.61 (d, 1H, H13), 3.65 (m, 1H, H11'), 3.76 (m, 1H, H11), 3.81 (m, 2H, H18), 5.00 (d, 1H, H10'), 5.16 (m, 1H, H10), 7.54 (s, 1H, Thy-H6), 8.26,

8.28 (s, 1H, Ade-H8), 8.36, 8.37 (s, 1H, Ade-H2), 8.37, 8.46 (brs, 2H, Ade-N6H₂), 11.30 (s, 1H, Thy-N3H); MS: *m/z*: 562.0 [Pd(1)Cl]⁺; elemental analysis (%) calcd for 2·3H₂O: C 28.99, H 4.12, N 13.92; found: C 28.13, H 3.97, N 13.14. A small quantity of crystals of **2** suitable for single-crystal X-ray diffraction studies were grown by slow cooling of a hot aqueous solution.^[9]

3: Same procedure as for Pd analogue **2**, except that K₂[PtCl₄] (0.074 g, 0.182 mmol) in aqueous solution was used as starting material, and to this was added dropwise a hot ethanolic solution of **1** (0.076 g, 0.182 mmol), and the mixture refluxed overnight. The cooled solution was taken to dryness under reduced pressure, and the resultant solid residue dissolved in hot water (50 mL). The mixture was filtered to remove undissolved solids and concentrated to a minimum volume in vacuo. The addition of a saturated aqueous solution of NaBF₄ precipitated **3** as a white solid, which was washed with water, ethanol, and diethyl ether and pump dried. Yield 0.093 g, 69.3%. ¹H NMR ([D₆]DMSO, TMS): δ = 1.78, 1.81 (s, 3H, Thy-CH₃), 2.13, 2.23 (m, 2H, H17), 3.04 (m, 1H, H16), 3.10 (m, 1H, H16), 3.22 (d, 1H, H13'), 3.36 (m, 1H, H14), 3.39 (m, 1H, H14'), 3.62 (d, 1H, H13), 3.73 (m, 1H, H11'), 3.82 (m, 1H, H11), 4.74 (m, 2H, H18), 4.81, 5.07 (d, 1H, H10'), 5.13 (m, 1H, H10), 7.51, 7.53 (s, 1H, Thy-H6), 8.28, 8.29 (s, 1H, Ade-H8), 8.41, 8.43 (s, 1H, Ade-H2), 8.47, 8.57 (brs, 2H, Ade-N6H₂), 11.29 (s, 1H, Thy-N3H); MS: *m/z*: 652.0 [Pt(1)Cl]⁺; elemental analysis (%) calcd for 3·2H₂O: C 26.35, H 3.51, N 12.65; found: C 27.07, H 3.98, N 12.71. Crystallization by slow cooling of a hot aqueous solution of **3** yielded a few single crystals, some of which were suitable for diffraction studies.^[9]

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- [8] a) Crystal data for **2**: C₁₇H₃₂ClF₃N₇O_{6.5}PdS₂Si_{0.5}, *M_r* = 715.51, monoclinic, space group *I2/a*, *a* = 24.3737(16), *b* = 7.9006(5), *c* = 29.2031(19) Å, β = 97.894(2)°, *V* = 5570.3(6) Å³, *Z* = 8, ρ_{calcd} = 1.706 g cm^{−3}, MoKα radiation, λ = 0.71073 Å, μ = 1.00 mm^{−1}, *T* = 160 K. 18467 measured reflections were corrected for absorption; 4903 were

unique (*R*_{int} = 0.0451, θ ≤ 25.0°); *R* = 0.0829 (*F* values, *F*² > 2σ), *R_w* = 0.1771 (*F*² values, all data), GOF 1.312 for 350 parameters, max./min. residual electron density 2.58/−1.47 e Å^{−3}. b) Crystal data for **3**: C₁₇H₃₂ClF₃N₇O_{6.5}PtS₂Si_{0.5}, *M_r* = 804.20, monoclinic, space group *I2/a*, *a* = 24.4619(10), *b* = 7.9190(3), *c* = 29.1288(10) Å, β = 98.073(2)°, *V* = 5586.7(4) Å³, *Z* = 8, ρ_{calcd} = 1.912 g cm^{−3}, synchrotron radiation at Daresbury Laboratory station 9.8, λ = 0.6942 Å, μ = 5.36 mm^{−1}, *T* = 160 K. 18024 measured reflections were corrected for absorption; 6866 were unique (*R*_{int} = 0.0360, θ ≤ 27.5°); *R* = 0.0388 (*F* values, *F*² > 2σ), *R_w* = 0.1053 (*F*² values, all data), GOF 1.185 for 350 parameters, max./min. residual electron density 2.49/−1.19 e Å^{−3}. c) The anion in both crystal structures was identified as SiF₆^{2−}, generated by etching of the glass by the aqueous BF₄[−] ions. Detailed evidence is available from the authors. d) Programs: standard Bruker AXS control and integration software and SHELXTL. CCDC-170471 (**2**) and CCDC-170472 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Dearomatizing Disrotatory Electrocyclic Ring Closure of Lithiated *N*-Benzoyloxazolidines**

Jonathan Clayden,* Savroop Purewal, Madeleine Helliwell, and Simon J. Mantell

Aromatic amides—both naphthamides and benzamides—can be dearomatized in a cyclization reaction triggered by a benzylic lithiation α to the amide nitrogen.^[1] The reaction has been optimized for the synthesis of functionalized cyclohexadienes **4** and cyclohexenones from amides **1**, and both the benzamide and naphthamide versions of the reaction (Scheme 1) have been employed in the synthesis of important members of the kainoid family of cyclic amino acids.^[2]

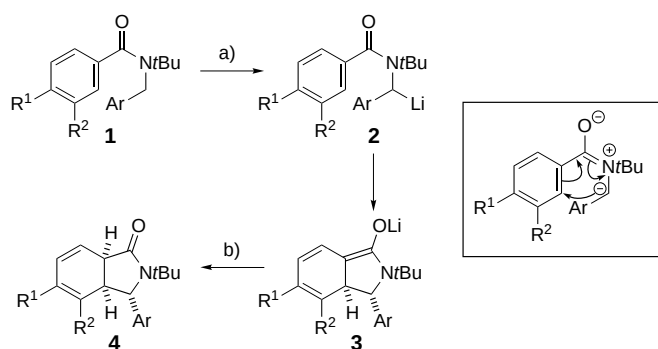
Superficially, the mechanism of this cyclization appears to be an intramolecular conjugate addition reaction^[3] of the benzylic anionic center into the electron-deficient *ortho* position of the aromatic ring, with the product stereochemistry arising from the preference of the phenyl group for the *exo* face of the forming bicyclic ring system. However, under this interpretation, the cyclization of the lithiated benzamide **2** has at least some (Baldwin-disfavored) 5-*endo-trig* character,^[4] and the cyclization of a 2-naphthamide **2** (*R*¹, *R*² = benzo) rather more.

An attractive alternative rationalization, illustrated in the box in Scheme 1, is that the cyclization is pericyclic and

[*] Prof. J. Clayden, S. Purewal, Dr. M. Helliwell
Department of Chemistry
University of Manchester
Oxford Rd, Manchester M13 9PL (UK)
Fax: (+44) 161-275-4939
E-mail: j.p.clayden@man.ac.uk

Dr. S. J. Mantell
Pfizer Central Research
Sandwich, Kent CT13 9NJ (UK)

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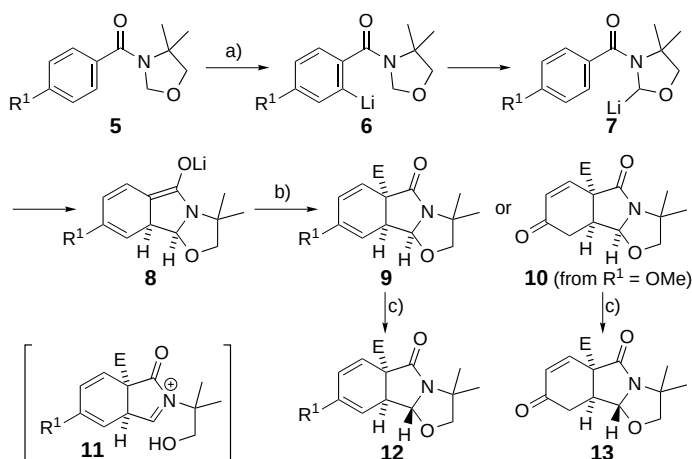
Scheme 1. Dearomatizing cyclization of lithiated *N*-aryl benzylamines. a) LDA, -78 – $+25$ °C; b) NH_4Cl .

therefore is not subject to the usual stereoelectronic constraints adumbrated by Baldwin.^[4] A disrotatory thermal electrocyclic ring closure of **2** obeys the Woodward–Hoffmann rules,^[5] and will lead to the correct stereochemistry of **3**, provided that the aryl ring starts *trans* to the *tert*-butyl group. Stereochemistry alone can therefore not distinguish between the two mechanisms of cyclization in this case.

However, when the nitrogen atom is within a ring, the stereochemistry of the product is diagnostic of the reaction mechanism. Herein, we describe the first dearomatizing anionic cyclization of a non-benzyl substituted benzamide, the stereochemistry of which gives strong evidence that the cyclization is pericyclic.

The *N*-benzoyl oxazolidines **5** ($\text{R}^1 = \text{H}$ and $\text{R}^1 = \text{OMe}$)^[6] were lithiated with *t*BuLi or *s*BuLi in the presence of 1,3-dimethylhexahydro-2-pyrimidinone (DMPU) at -78 °C (Scheme 2). The resulting deep orange organolithium compounds were either warmed to 0 °C over 2 h (method A) or stirred at -78 °C for 14–16 h (method B). From **5** ($\text{R}^1 = \text{H}$) a tricyclic product **9** was obtained as a single diastereoisomer in moderate to good yield (Table 1).^[7] Enones **10** were obtained from **5** ($\text{R}^1 = \text{OMe}$) after work up with 1 M HCl. The structure of **9a** was established by X-ray crystallography^[8] (Figure 1 a), while evidence for the stereochemistry of **9b–d**, **10a** and **10b** (Table 1) was gained from nuclear Overhauser enhancement (NOE) studies (Figure 2 and Table 1).

On stirring **9b–d** or **10b** with acid (2 M HCl in ether), a clean isomerization took place to yield a diastereoisomer **12b–d** quantitatively (or enone **13** from **10b**), presumably via the acyliminium ion **11**. An X-ray crystal structure^[8] (Figure 1 b) of **12c** confirmed its stereochemistry, and NOE



Scheme 2. Dearomatizing cyclization of lithiated *N*-benzoyl oxazolidines **5**; a) Method A: *s*BuLi or *t*BuLi (1.5 equiv), DMPU (6 equiv), THF, -78 °C, 30 min then 0 °C, 2 h or Method B: *t*BuLi (1.5 equiv), DMPU (6 equiv), THF, -78 °C, 14–16 h; b) E^+ ; c) 2 M HCl, MeOH or Et_2O .

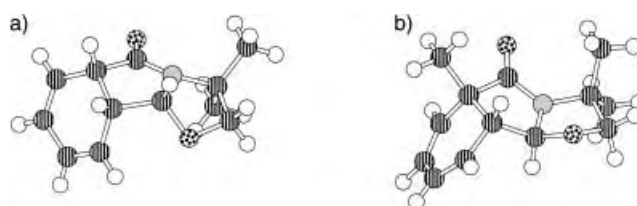


Figure 1. a) X-ray crystal structure of **9a**; b) X-ray crystal structure of **12c**.

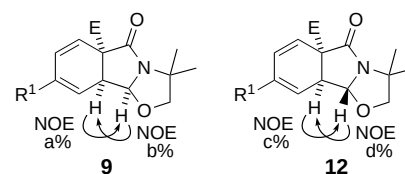


Figure 2. Stereochemistry of **9** and **12**.

studies (Figure 2) confirmed the stereochemistry of **12b–d** and **13**. Evidently the initial cyclization produces a *cis*-fused tricyclic ring system which is significantly less stable than the *trans*-fused system formed after epimerization under thermodynamic control.

While an ionic cyclization of lithiated **5** would be expected to generate directly a more stable *trans* tricyclic enolate *epi*-**8**, and hence **12**, thermal electrocyclic ring closure of lithiated **5** must be disrotatory and therefore has no alternative but to form the enolate **8** with a *cis* tricyclic structure (Scheme 3). The stereochemistry of the product strongly suggests that the

Table 1. Yields and Stereochemistry.

Entry	R^1	E^+	E	Yield 9 ^[a] or 10 ^[b] [%]	NOE a %	NOE b %	Yield 12 or 13 [%]	NOE c %	NOE d %
1	H	NH_4Cl	H	9a 60	–	–	–	–	–
2	H	CD_3OD	D	9b 60	20.0	22.3	12b 13 ^[c]	2.2	2.5
3	H	MeI	Me	9c 53 ^[d]	13.2	17.3	12c 100	2.3	1.8
4	H	BnBr	Bn	9d 45	14.6	11.2	12d 99	4.1	2.9
5	H	PBB-Br ^[e]	PBB	9e 41	–	–	–	–	–
6	MeO	1 M HCl	H	10a 55	14.9	13.5	–	–	–
7	MeO	MeI then 1 M HCl	Me	10b 48	12.5	13.8	13 100	3.7	2.6

[a] From **5** ($\text{R}^1 = \text{H}$) by method A. [b] From **5** ($\text{R}^1 = \text{OMe}$) by method B. [c] Major product is **19** ($\text{E} = \text{H}$). [d] By NMR. [e] PBB = *p*-BrC₆H₄CH₂.

Click Chemistry In Situ: Acetylcholinesterase as a Reaction Vessel for the Selective Assembly of a Femtomolar Inhibitor from an Array of Building Blocks**

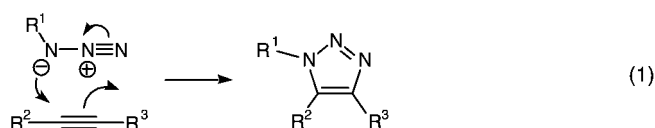
Warren G. Lewis, Luke G. Green, Flavio Grynszpan, Zoran Radić, Paul R. Carlier, Palmer Taylor, M. G. Finn,* and K. Barry Sharpless*

The generation and/or optimization of lead compounds by combinatorial methods has become widely accepted in medicinal chemistry, and is the subject of continued improvement.^[1–3] However, most combinatorial strategies remain dependent upon iterative cycles of synthesis and screening. The direct involvement of the target, usually a receptor or enzyme, in the selection, evolution, and screening of drug candidates can accelerate the discovery process by short-circuiting its traditionally stepwise nature.^[4–11]

The use of an enzyme target to select building blocks and synthesize its own inhibitor is a relatively unexplored option. This approach depends on the simultaneous binding of two ligands, decorated with complementary reactive groups, to adjacent sites on the protein; their co-localization is then likely to accelerate the reaction that connects them.^[12] When the catalysis of such bond formation is blocked by product inhibition, the higher affinity products^[12–14] then serve as lead compounds. This and similar approaches that have been adopted by a number of investigators employ one of five types

of connecting reactions: formation of hydrazone or Schiff base adducts, disulfide bond formation, alkylation of free thiols or amines, epoxide ring-opening, or olefin metathesis.^[5, 6, 8, 11, 15–19] Most closely related to the work described herein is the generation of carbonic anhydrase inhibitors by using the S_N2 reaction of a thiol with an α -chloroketone in the presence of the enzyme target.^[16]

Most of the above strategies share the limitation that the reactive groups on the ligand probes (building blocks), being either electrophiles or nucleophiles, are likely to react in undesired ways within biochemical systems. An alternative is offered by the “cream of the crop” among “click reactions”^[20]—the Huisgen 1,3-dipolar cycloaddition of azides and alkynes to give 1,2,3-triazoles [Eq. (1)].^[21–23] This water-



tolerant reaction employs functional groups that are generally compatible with enzymes under physiological conditions^[24, 25] and are readily incorporated into diverse organic building blocks. Its dependence on the enforced propinquity and proper alignment of the reactants, which gives rise to large negative values of $\Delta S^\ddagger$, makes it ideal for the purpose at hand. Mock and co-workers established that the rate and regioselectivity of the azide–alkyne cycloaddition can be dramatically enhanced by sequestering the two components inside a host structure.^[26–29] Their results with cucurbituril ($M_w = 997$ Da) as the catalyst in water bear an uncanny resemblance to those reported here for reaction inside a protein host.

We selected the enzyme acetylcholinesterase (AChE), which plays a key role in neurotransmitter hydrolysis in the central and peripheral nervous systems,^[30, 31] as the target. AChE contains a narrow gorge approximately 20 Å in depth, lined with aromatic side chains.^[32, 33] The active center, comprised of the acylation and choline-binding sites, is located at the gorge base; a “peripheral” site is found at its rim. Small-molecule ligands for each of these sites are known, and inhibitors that span the active center and the peripheral site have also been shown to exhibit tighter binding than the individual components.^[34–39]

As a proof of principle AChE was used to select and synthesize a triazole-linked bivalent inhibitor by using known site-specific ligands as building blocks. A selection of site-specific inhibitors based on tacrine^[38, 40] and phenanthridinium^[38, 41] motifs decorated with alkyl azides and alkyl alkynes of varying chain lengths (Scheme 1) was prepared by variations of known methods.^[40, 42, 43] Although reversible AChE inhibitors are used clinically to treat Alzheimer’s dementia,^[44] *these compounds should be handled with care, since high-affinity inhibitors are potentially neurotoxic.* The building blocks shown in Scheme 1 allow for the presentation of 98 potential bivalent inhibitors to AChE: 34 regioisomeric pairs (*syn* and *anti* triazoles) of mixed tacrine/phenanthridinium adducts (**TZ2–6/PA2–6** and **TA1–3/PZ6–8**) and 15

[*] Prof. M. G. Finn, Prof. K. B. Sharpless, W. G. Lewis, Dr. L. G. Green
Department of Chemistry
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-7562
E-mail: mgfinn@scripps.edu, sharpless@scripps.edu

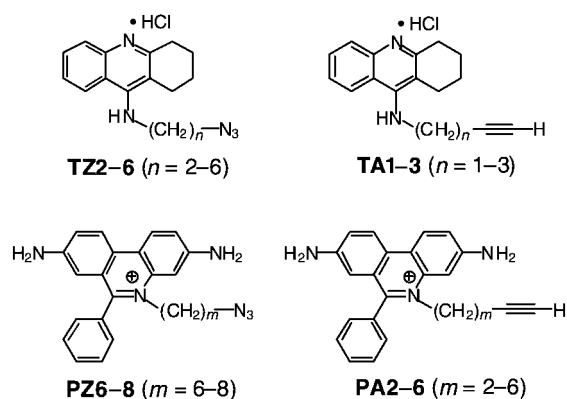
Prof. F. Grynszpan
Department of Molecular Biology
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037 (USA)

Dr. Z. Radić, Prof. P. Taylor
Department of Pharmacology
University of California San Diego
La Jolla, CA 92093-0636 (USA)

Prof. P. R. Carlier
Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, VA 24061 (USA)

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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. Azide and alkyne building blocks. Key: T=tacrine, P=phenanthridinium, A=alkyne terminus, Z=azide terminus, n, m =number of CH_2 units in the chain connecting the binding and reactive moieties.

regioisomeric pairs of tacrine/tacrine triazoles (**TA1-3/TZ2-6**).^[45] Each of the possible binary mixtures was incubated in the presence of *Electrophorus* AChE at room temperature.^[46] The rate of reaction under these conditions in the absence of enzyme is negligible,^[47] so detectable amounts of triazole products should form only when the azide and alkyne are brought together by the enzyme. Therefore, product formation is a direct indication of a potential “hit”.

Examination of the 49 reactions by DIOS mass spectrometry^[48, 49] showed only one combination, **TZ2** + **PA6**, in which a detectable amount of the corresponding triazole (compound **1**) was produced, an observation confirmed for a subset of reactions by more cumbersome HPLC-MS methods.^[39] Control experiments established that blocking of the enzyme active center in either covalent or noncovalent fashion inhibits the formation of triazole **1**^[39] which demonstrates that the binding cleft of AChE serves as a template for the 1,3-dipolar cycloaddition reaction. Furthermore, it was found that 2 ± 1 equivalents of triazole were made per equivalent of active enzyme^[39] which suggests that the adduct was bound tightly by AChE.

Authentic samples of triazoles from seventeen of the possible azide-alkyne combinations were prepared by heating the components together at 80°C in the absence of solvent for six days. The products were obtained in high yield, typically as equimolar mixtures of the *syn* (1,5-triazole) and *anti* (1,4-triazole) regioisomers. When desired, the regioisomers were separated by HPLC and independently characterized by MS and $^1\text{H-NMR}$ (nOe). Comparison of the HPLC traces of the enzyme-templated product and the authentic mixture of *syn*- and *anti*-**1** (from thermal cycloaddition between **TZ2** and **PA6** in the absence of enzyme) revealed that the in situ reaction generates predominantly the *syn* isomer (Figure 1).

Detailed kinetic analyses of the binding and inhibitory properties of *syn*- and *anti*-**1** against *Electrophorus*, *Torpedo*, and mouse AChE were performed by using both stopped-flow^[50] and conventional (Ellman assay^[51]) techniques (Table 1).^[39, 52] Dissociation constants (K_d) of *syn*-**1** of 77 to 410 femtomolar (fM) were found, depending on the species, which makes it the most potent noncovalent AChE inhibitor known to date by approximately two orders of magnitude.^[53, 54] The *anti*-**1** isomer exhibited K_d between 720 fM and 14 pM, a value as much as 140 times larger than that of the *syn* compound. Thus, the more active *syn*-triazole regioisomer is the same structure that is preferentially assembled by the enzyme.

The dissociation constants for both *syn*- and *anti*-**1** are substantially lower (i.e. higher affinity) than their components (10–100 nM for tacrine and low μM for propidium). We find that both isomers access the enzyme at rates similar to each other and to tacrine, but differ in their rates of dissociation (off-rates), with that for *syn*-**1** being extremely slow. In addition to the entropic benefits expected from tethering two binding elements to each other, the linker assembly, which

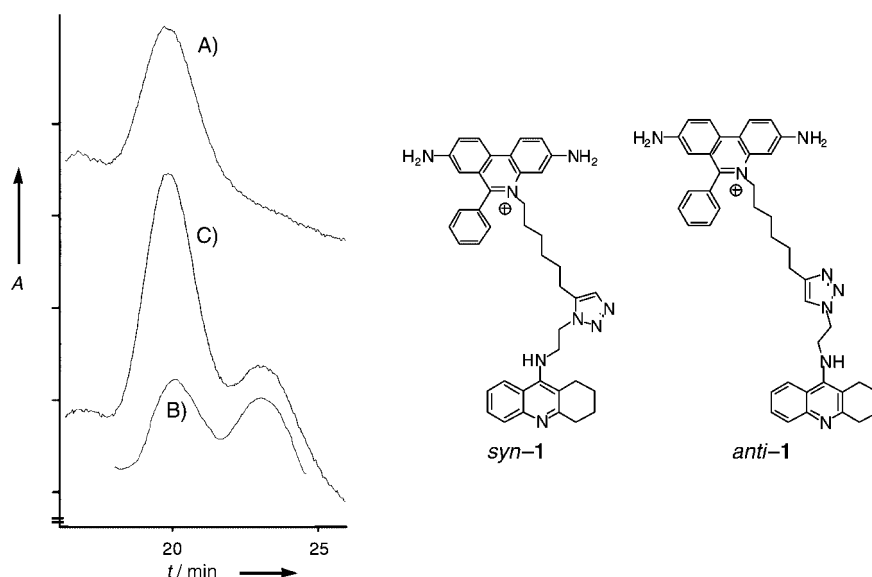


Figure 1. Left: HPLC analysis of thermal and AChE-templated assembly of **TZ2** and **PA6**. A) Product from in situ assembly in the presence of AChE. B) Triazole **1** prepared by thermal reaction; equal amounts of *syn* and *anti* isomers were isolated. C) Solution (A) plus a small amount of solution (B). Right: *syn*- and *anti*-isomers of **1**.

Table 1. Kinetic parameters derived for binding of **1**, and literature data for related noncovalent inhibitors of AChE from various species.

Inhibitor	k_{on} [$10^{10}\text{M}^{-1}\text{min}^{-1}$]	k_{off} [min^{-1}]	K_d	AChE source
<i>syn</i> - 1	1.5	0.0015	99 fM	<i>E. electricus</i>
	1.3	0.0011	77 fM	<i>T. californica</i>
	1.3	0.0079	410 fM	mouse
<i>anti</i> - 1	1.8	0.25	14 000 fM	<i>E. electricus</i>
	3.2	0.026	720 fM	<i>T. californica</i>
	2.4	0.30	8900 fM	mouse
tacrine ^[38]	0.78	138	18 nM	mouse
propidium ^[38]	1.4	15000	1100 nM	mouse
huprine X ^[55]	0.044	0.009	26 pM	human
ambenonium ^[35]	0.31	0.78	250 pM	human

consists of the two methylene chains and the triazole, may also interact favorably with the enzyme.

Docking of *anti* and *syn*-1 in AChE from *Torpedo californica* (PDC code 1ACJ with Trp279 adopting the conformation found in 1ACL) with the program AutoDock v.3.05^[56] shows that the tacrine portion of the inhibitor can be accommodated at the bottom of the active center gorge (practically superimposed on tacrine in the crystal structure), while the phenanthridinium piece is likely to be located in the peripheral site at the rim of the gorge (Figure 2). Interestingly, the triazole moiety is predicted to lie below (deeper than) the narrowest point of the gorge (defined by Phe330, Tyr334, Phe331, Phe288, Trp233, Phe290, and Tyr121).^[57]

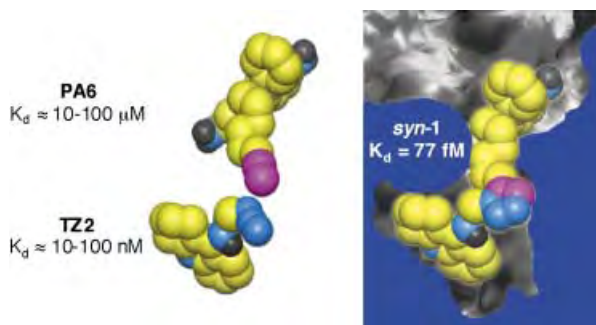


Figure 2. Left: **TZ2** and **PA6** components used for in situ assembly of **1**. The estimated binding constants to AChE shown are those of the tacrine and propidium, respectively, which lack azide or alkyne functional groups. Right: Clipping plane (blue) revealing the *T. californica* AChE active center gorge. The lowest-energy docked conformer of *syn*-1 is shown. Alkyne and triazole carbon atoms appear in pink, nitrogen atoms in blue, and nitrogen-bound H atoms in black; all other H atoms are omitted for clarity.

It is apparent that the narrow confines of the AChE gorge impart high selectivity to the assembly reaction. For example, a preliminary survey of the relative potency of a selection of adducts made by thermal 1,3-dipolar cycloaddition as described above shows that the connectivity of the triazole does not seem to be as important as its position (both **TZ2/PA6** (**1**) and **TA2/PZ6** are highly potent, but **TZ6/PA2** is not). While we suspect that the unique adduct preferentially assembled by the enzyme (i.e., *syn*-1) is also likely to be the strongest inhibitor among the 98 triazoles which could have been synthesized, further measurements are in progress to confirm or refute this hypothesis.

We have shown that an enzyme can select and synthesize an extremely potent inhibitor from a parallel array of building blocks by using 1,3-dipolar cycloaddition reactions. This process, which is distinguished by its slow background rate and biocompatibility, provides an excellent probe of the AChE binding landscape. Function can be developed in situ as the individual blocks explore the biomolecular target for recognition elements. A permanent nexus in the form of the robust triazole linkage is made only when two cross-reactive blocks find themselves temporarily moored at adjacent sites, locking in topological and/or dynamic information about the biostructure which recruited them.

We anticipate that “false positives” will be relatively rare in the “in situ” approach. Assuming that the enzyme active site

or an important allosteric site is the template, and that the background rate of the reaction that connects the blocks is low, the formation of a bond between two blocks in situ virtually guarantees that the resulting adduct will be a valuable hit or lead compound for enzyme inhibition. A potential disadvantage of the application of “in situ” click chemistry to inhibitor discovery is the possibility of “false negatives” (effective inhibitors that are not assembled in the enzyme). Improvements in analytical methods and adjustments in the background rate of reaction of the components will help alleviate this problem.

In principle, target-directed assembly of inhibitors could be monitored by assays of enzyme activity instead of detection of the linked inhibitor molecule. In our view, such screening for function, when feasible, is almost always preferred. However, when function is difficult to measure in high-throughput fashion, the detection of potential inhibitors formed by the target is an attractive alternative, as demonstrated here. This latter approach should also facilitate true combinatorial experiments, in which multiple candidate blocks are incubated with the target.

In general, the in situ and traditional (screening of prefabricated candidates) methods of discovery are complementary, and tend to merge with the use of increasingly reliable synthetic transformations. That such a potent inhibitor as *syn*-1 was found directly by using the azide–alkyne cycloaddition to unite the probe molecules is interesting, but its broad utility as a search tool remains to be established. Nevertheless, the special qualities of this reaction bode well for its use in creating or amplifying function.

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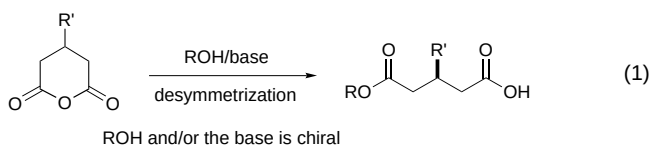
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Highly Enantioselective Desymmetrization of Anhydrides by Carbon Nucleophiles: Reactions of Grignard Reagents in the Presence of (–)-Sparteine**

Ryo Shintani and Gregory C. Fu*

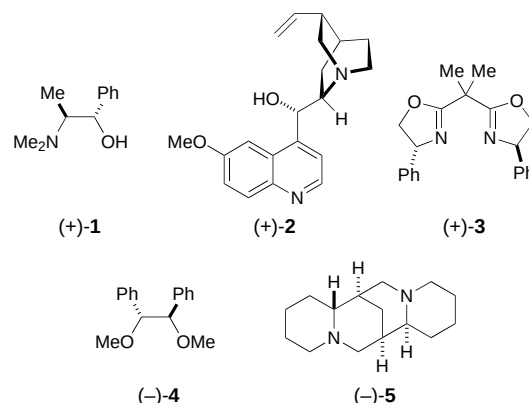
The desymmetrization of *meso* and other prochiral compounds represents a powerful approach to asymmetric synthesis,^[1] and a number of enantioselective total syntheses have been based on this strategy.^[2] The desymmetrization of anhydrides has been a particular focus of interest. Most investigations of this family of substrates have employed an alcohol as the nucleophile^[3] [for example, a chiral alcohol^[4] or an achiral alcohol in combination with a chiral catalyst,^[5] Eq. (1)]. In addition, success has been reported for reactions with a stoichiometric quantity of an enantiopure reducing agent^[6] or amine.^[7]



On the other hand, very little progress has been described for the desymmetrization of anhydrides with carbon-based nucleophiles. In fact, to the best of our knowledge, only one report has begun to successfully address this challenge, a study by Real and co-workers that focused on the reaction of a

single substrate, a bicyclic anhydride, with Grignard reagents bearing chiral oxazolidine auxiliaries.^[8] In an attempt to remedy this methodological deficiency, we have recently initiated an investigation of the desymmetrization of anhydrides by carbon nucleophiles. Rather than covalently attaching a chiral auxiliary to the nucleophile and then releasing it, we chose to concentrate our efforts on the use of chiral ligands as the source of asymmetry. Here we report that (–)-sparteine-bound Grignard reagents effectively desymmetrize an array of cyclic anhydrides to furnish ketoacids in very good enantiomeric excess.

In our initial work, we decided to explore the ring-opening of 3-phenylglutaric anhydride by phenylmagnesium chloride. We examined a structurally diverse set of chiral ligands (Scheme 1) that have proved useful in a number of other



Scheme 1. Ligands used in preliminary experiments.

enantioselective processes, including a simple aminoalcohol (Table 1, entry 1), a cinchona alkaloid (entry 2), a bisoxazoline (entry 3), and a dimethyl ether (entry 4). Disappointingly, all were rather ineffective at desymmetrizing the anhydride (< 40% *ee*). Fortunately, however, we discovered that readily available (–)-sparteine accomplishes the ring opening with high enantioselectivity (88% *ee*; entry 5).

Of course, we are not the first to document the remarkable capacity of (–)-sparteine to control enantioselection. Pioneering observations by Nozaki et al. in the 1960's^[9] have been followed by fascinating studies by a number of groups, including those of Hoppe and Beak.^[10, 11] The large majority

Table 1. Desymmetrization of 3-phenylglutaric anhydride by PhMgCl: a survey of chiral ligands.^[a]

Entry	Ligand	<i>ee</i> [%]	Yield [%]
1 ^[b]	(+)- 1	1	76
2 ^[b]	(+)- 2	12	76
3	(+)- 3	32	66
4	(–)- 4	39	77
5	(–)- 5	88	63

[a] All data are the average of two runs. [b] 2.0 equiv of PhMgCl was used.

[*] Prof. Dr. G. C. Fu, R. Shintani
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-258-7500
E-mail: gcf@mit.edu

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of these investigations have focused on the use of (–)-sparteine to achieve asymmetric reactions of organolithium reagents. The result described in Table 1, entry 5, represents a rare example in which (–)-sparteine furnishes very good enantiocontrol for a reaction of a Grignard reagent.^[12, 13]

For the desymmetrization of 3-phenylglutaric anhydride by PhMgCl, we subsequently determined that the use of a slight excess of Grignard reagent/(–)-sparteine leads to an enhancement in stereoselectivity (88% *ee* → 92% *ee*) and an improvement in yield (63% → 91%; entry 5 of Table 1 vs. entry 1 of Table 2). Under these conditions, a change in the electronic nature of the Grignard reagent has a relatively moderate influence on enantioselection (Table 2, entries 1–3), whereas an increase in the steric demand has a very substantial impact (entry 1 vs. entry 4).

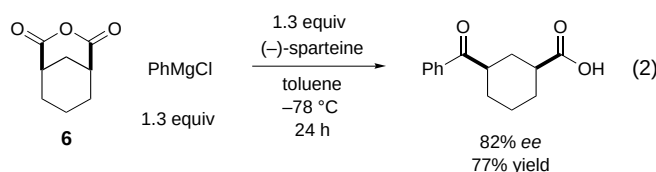
Table 2. Desymmetrization of 3-phenylglutaric anhydride: a survey of Grignard reagents.^[a]

Entry	ArMgX	<i>ee</i> [%]	Yield [%]
1 ^[b]	PhMgCl	92	91
2	<i>p</i> -MeOC ₆ H ₄ MgBr	89	88
3	<i>p</i> -FC ₆ H ₄ MgBr	78	82
4	<i>o</i> -TolMgCl	37	66

[a] All data are the average of two runs. Ring openings in toluene provide higher *ee* than reactions in Et₂O or THF. At temperatures above –78 °C, slightly lower enantioselection is observed. [b] PhMgBr and PhMgCl furnish the same level of enantioselectivity.

We have also investigated the scope with respect to the anhydride, and we have established that the reaction tolerates a wide range of substituents and provides uniformly high *ee* values (Table 3). Thus, substrates that bear hindered aromatic (88% *ee*; entry 2) and heteroaromatic groups (91% *ee*; entry 3) undergo desymmetrization with good enantioselectivity. Benzyl-substituted (92% *ee*; entry 4), as well as a sterically diverse array of alkyl-substituted (90–92% *ee*; entries 5–8), anhydrides react to furnish ketoacids with excellent enantioselectivity. The enantioselective ring-opening of heteroatom-substituted anhydrides also proceeds with high stereoselection (87% *ee*; entry 9).

We can effectively desymmetrize not only monocyclic, but also bicyclic anhydrides. Thus, meso **6** reacts with PhMgCl/(–)-sparteine to generate the chiral ketoacid in good enantiomeric excess [Eq. (2)].



In summary, we have described the first enantioselective desymmetrizations of anhydrides with carbon-based nucleo-

Table 3. Desymmetrization of anhydrides: scope.^[a]

Entry	R	<i>ee</i> [%]	Yield [%]
1		92	91
2		88	87
3		91	74
4		92	87
5		90	74
6		91	76
7		92	70
8		91	84
9 ^[b]	TBSO-	87	51

[a] All data are the average of two runs. [b] TBS = *tert*-butyldimethylsilyl.

philes by employing (–)-sparteine as a chiral ligand. These C–C bond-forming reactions proceed in good enantioselectivity for a range of anhydrides. To the best of our knowledge, this is the first general method wherein (–)-sparteine, which exhibits remarkable versatility in enantioselective reactions of organolithium compounds, has provided excellent stereocontrol in reactions of Grignard reagents. We anticipate that this discovery will stimulate a wide array of studies of applications of (–)-sparteine-complexed Grignard reagents in asymmetric synthesis.

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A Stereospecific Ruthenium-Catalyzed Allylic Alkylation**

Barry M. Trost,* Pierre L. Fraise, and Zachary T. Ball

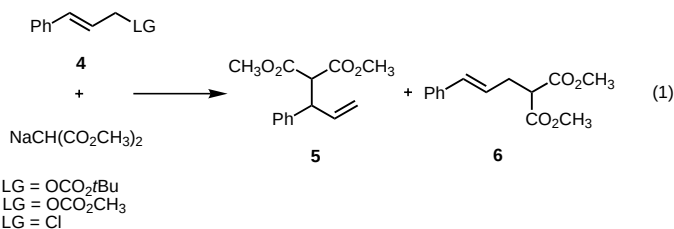
Metal-catalyzed allylic alkylations provide a powerful tool for the construction of complex molecules. One of the benefits of such substitutions is the prospect that the regioselectivity with unsymmetrical allyl substrates can be controlled by the catalyst rather than the position of the allylic substituent serving as the leaving group. Palladium-catalyzed allylic

alkylations normally favor nucleophilic addition to the less substituted allyl terminus although ligands can influence this selectivity.^[1] Early results demonstrate the effectiveness of $\text{Mo}^{[3]}$ and $\text{W}^{[4]}$ catalysts and, more recently, their ability to induce enantioselectivity.^[5] Such catalysts normally do not work with heteroatom nucleophiles. Iridium catalysts have been reported to favor attack on the more substituted carbon with a carbon—and most recently nitrogen—nucleophile, but the use of an oxygen nucleophile like phenol has not been reported.^[6] Rhodium catalysis has proven to be very interesting in that the regioselectivity of the substitution is determined by the position of the leaving group.^[7] Herein, we report our preliminary observations that the ruthenium-catalyzed reaction favors attack at the more substituted carbon atom regardless of the regioisomeric nature of the substrate and does so with complete retention of enantiomeric purity when a chiral scalemic substrate is employed. This study has led to a facile synthetic strategy to antidepressants like fluoxetine,^[8] the active ingredient of prozac, from ephedrine.

Pioneering work in ruthenium-catalyzed allylic alkylation by Watanabe et al. with the $[\text{Ru}(\text{cod})(\text{cot})]$ ($\text{cod} = 1,5\text{-cyclooctadiene}$; $\text{cot} = 1,3,5\text{-cyclooctatriene}$) complex has indicated a bias for attack at the more substituted terminus with some nucleophiles, although only a 50:50 regioisomeric mixture was obtained by using a cinnamyl carbonate and malonate anion.^[9] $[\text{CpRu}(\text{cod})\text{Cl}]^{[10]}$ (**1**) and $[\text{CpRu}(\text{PPh}_3)_2\text{Cl}]^{[11]}$ (**2**) have been employed together with heteroatom nucleophiles, but the regioselectivity has not been satisfactorily addressed.

Our recent work on cyclocondensations of allenes and vinyl ketones using $[\text{CpRu}(\text{NCCH}_3)_3]\text{PF}_6$ (**3**) induced us to examine this complex as a catalyst for regioselective allylic alkylation.

We chose the reaction shown in Equation (1) as a standard. In contrast to the earlier reports in which **1** or **2** were used and which required elevated temperatures, complex **3** effected the



reaction of carbonate **4a** at ambient temperature in DMF to give a 1:2 ratio of **5:6** in nearly quantitative yield. Attempts to increase this selectivity by varying the reaction conditions failed and thus we examined changes in the ligand. We reasoned that a more sterically demanding catalyst might favor the monosubstituted olefin adduct initially formed from “branched” attack to afford **5**. Under identical conditions with carbonate **4a**, $[\text{Cp}^*\text{Ru}(\text{NCCH}_3)_3]\text{PF}_6$ (**7**) ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) gave a 9:1 ratio of **5:6** (96% yield) in 2 h. In acetone, the selectivity increased to 19:1 (quantitative yield). Reactions of the methyl carbonate **4b** are generally faster. Indeed, in DMF within 30 min, a quantitative yield of alkylation products was obtained in a 14:1 ratio of **5:6** with only 1 mol % of catalyst **7**.

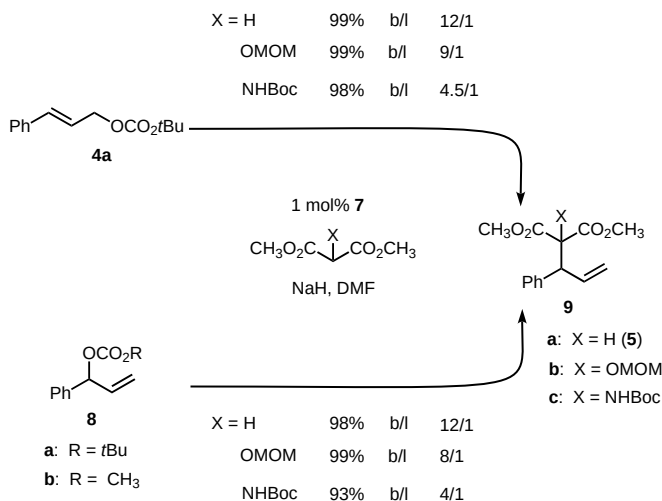
[*] Prof. B. M. Trost, P. L. Fraise, Z. T. Ball
Department of Chemistry
Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0002
E-mail: bmtrost@stanford.edu

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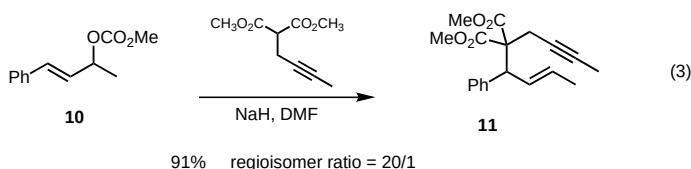
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Cinnamyl chlorides (**4c**) are also effective electrophiles. Although poor regioselectivity is observed at ambient temperature, at -40°C in DMF, a quantitative yield of virtually pure **5** (**5**:**6** 110:1) was obtained.

The regioselectivity as a function of the regioisomeric allylic carbonates **4a** and **8** was examined with a series of malonates [Eq. (2); b = branched, l = linear]. Very similar

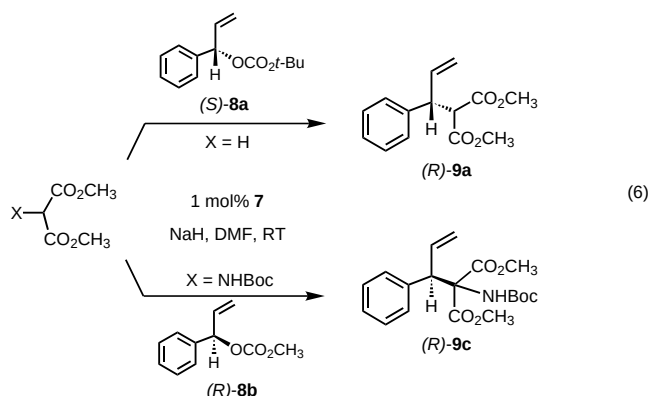
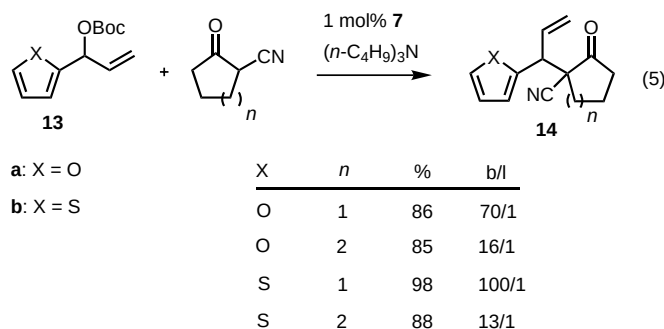
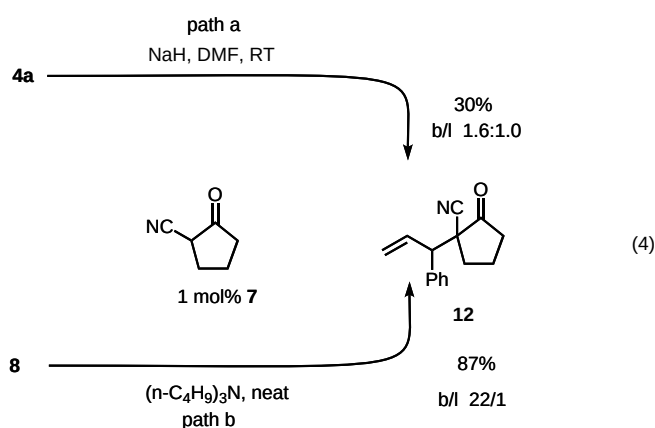


results were obtained with three different malonates, whereby the branched product **9** was strongly favored. To a first approximation these results support the postulate of a π -allylruthenium intermediate. Catalyst-controlled regioselectivity is further demonstrated for an unsymmetrical, disubstituted allyl unit [Eq. (3)], for which excellent preference for

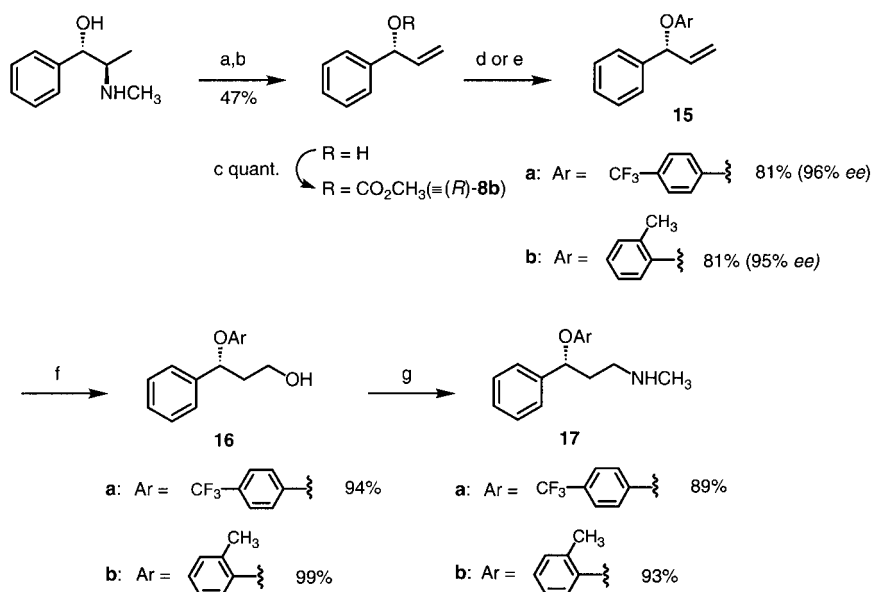


the benzylic position is observed for an allylic carbonate of opposite regiochemistry. Unfortunately, direct extension to α -cyanocyclopentanone led to a sluggish reaction (30% conversion after 4 h) and poor regioselectivity (b/l 1.6:1) [Eq. (4), path a]. This problem was resolved in a most gratifying fashion—by simply running the reaction without solvent using tri-*n*-butylamine as base and with **8** as the substrate [Eq. (4), path b]. These neat conditions proved general for bulkier nucleophiles, and Equation (5) illustrates the applicability of heteroaryl substrates **13**. Notably, diastereoselection has not been observed for the unsymmetrical β -keto ester nucleophiles. Yields given are for an approximately 1:1 mixture of (sometimes separable) diastereomers.

Having established the involvement of a functional equivalent of a π -allylruthenium intermediate, we examined the stereochemistry of the substitution by using chiral substrate **8** of high enantiopurity [Eq. (6)]. Starting with (*S*)-**8a** of 94% *ee* gave (*R*)-**9a** of 94% *ee*, therefore constituting com-



plete chirality transfer (CT). The absolute configuration was established by comparison with a known sample. Similarly, starting with the enantiomeric substrate (*R*)-**8b** of 99% *ee* with the amidomalonate gave the epimeric product (*R*)-**9c** of 99% *ee*, again constituting 100% CT. Thus, ionization occurs to generate cleanly only one enantiomeric π -allylruthenium complex that does not equilibrate under the reaction conditions. We next sought to extend the scope of our enantio-specific alkylation to O-nucleophiles in the context of the synthesis of the antidepressants (*R*)-fluoxetine^[8] and (*R*)-tomoxetine from (*S*)-ephedrine as shown in Scheme 1.^[12] The starting allyl alcohol was available by Hoffmann elimination of the quaternary ammonium salt derived from ephedrine using strong base.^[13] Both enantiomers of the allyl alcohol are readily available from the corresponding commercial ephedrine. The free phenol was not a satisfactory nucleophile, but its silyl ether in the presence of a catalytic amount of a



Scheme 1. Synthesis of antidepressants. a) CH_3I , K_2CO_3 , CH_3OH , RT; b) LDA, THF, HMPA, -50 to 0°C ; c) $n\text{-C}_4\text{H}_9\text{Li}$, ClCO_2CH_3 , THF, -78 to 0°C ; d) 1 mol % **7**, $p\text{-CF}_3\text{C}_6\text{H}_4\text{OTMS}$, 1 mol % TBAT, neat, 35°C ; e) 1 mol % **7**, $o\text{-CH}_3\text{C}_6\text{H}_4\text{OTMS}$, 5 mol % ($n\text{-C}_4\text{H}_9$)₄NCl, 10 mol % (C_2H_5)₃N, neat, 35°C ; f) 9-BBN-H, THF, 35°C then KOH, H_2O_2 , 0°C ; g) $\text{CH}_3\text{SO}_2\text{Cl}$, (C_2H_5)₃N, CH_2Cl_2 , 0°C then CH_3NH_2 , CH_3OH , 70°C . LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, 9-BBN-H = 9-borabicyclo[3.3.1]nonane.

desilylating agent (tetrabutylammonium triphenyldifluorosilicate (TBAT) or tetrabutylammonium chloride (TBAC)) with 1 mol % of **7** under neat conditions effected the desired reaction. The reaction of the trimethylsilyl ether of *p*-trifluorocresol gave a 7:1 b/l ratio from which **15a** was isolated in 81 % yield.

Standard hydroboration, oxidation, and substitution provided (–)-fluoxetine (**17**). Switching to the *o*-cresol system similarly gave a 6:1 b/l ratio from which **15b** was isolated in 81 % yield. In both cases, excellent chirality transfer is observed, demonstrating the effectiveness of our catalyst for both carbon and heteroatom nucleophiles.

The ruthenium-catalyzed allylic alkylation differs from previous catalytic systems in several important respects. Like Pd, Mo, and W—but unlike Rh—regioselectivity is not highly dependent on the nature of the starting carbonate. Unlike Pd and Mo, but like Rh and W, substitution of the scalemic chiral substrate occurs with high net retention of configuration. Heteroatom nucleophiles which fail with Mo and W succeed with this system. Thus, this catalyst nicely complements the previously developed systems. Importantly, reactions proceed extremely well under mild conditions with 1 mol % of catalyst. The solvent-free conditions are commensurate with the ideals of green chemistry. The practicality of the methodology is illustrated by a novel synthesis of (*R*)-fluoxetine and (*R*)-tomoxetine starting from inexpensive ephedrine using a heretofore unknown elimination to generate the allyl alcohol of high enantiopurity.

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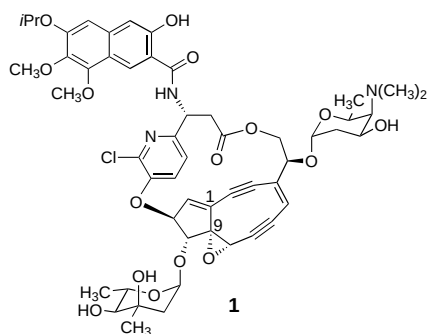
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Enantioselective Synthesis of Kedarcidin Chromophore Aglycon in Differentially Protected Form**

Andrew G. Myers,* Philip C. Hogan,
Alexander R. Hurd, and Steven D. Goldberg

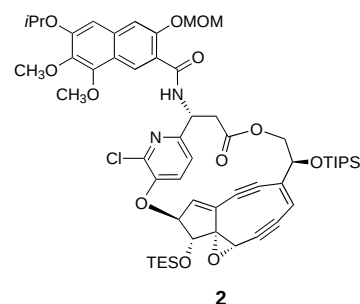
Kedarcidin is a highly reactive and complex chromoprotein enediyne natural product with potent antiproliferative and antibiotic activities.^[1] It is a member of the subset of enediyne antibiotics that includes neocarzinostatin,^[2] C-1027,^[3] macromycin,^[4] actinoxanthin,^[5] and maduropeptin.^[6] Each of these agents is composed of protein and small-molecule (chromophore) components, which form a 1:1 complex. The chromoprotein agents are thus distinguished from the nonproteinaceous (10-membered) cyclic enediyne agents (calicheamicin γ_1 , esperamicin, and dynemicin A),^[7] and further by the fact that their chromophoric components, when separated from the binding protein, are exceedingly unstable. Kedarcidin chromophore (**1**) has extremely limited



stability in solution and has been shown to undergo spontaneous cycloaromatization in the presence of sodium borohydride.^[1d] These issues of reactivity, coupled with structural features such as the chloropyridine-containing ansa-bridge, the highly unusual epoxy bicyclo[7.3.0]dodecadienediyne core, and the appended naphthoic acid amide, kedarose, and mycarose substituents, contribute to make the synthesis of **1** a formidable challenge. In addition to our own efforts to develop a synthesis of **1**, the Hirama group has reported the synthesis of core models,^[8a] an ansa-bridged macrolactone model,^[8b] and subsequent glycosylation studies of this macrolactone model structure.^[8c]

In a new strategy for the synthesis of the reactive core structures of the chromoprotein enediyne agents, we recently described the synthesis of a model compound that comprises the epoxy bicyclo[7.3.0]dodecadienediyne core functionality

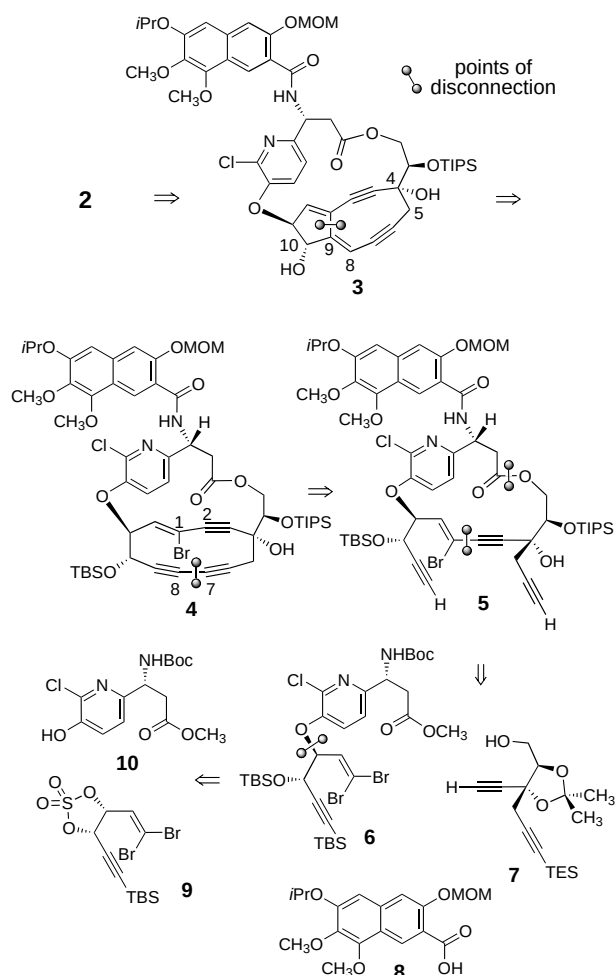
of **1**. This route targeted the C1–C9 fusion bond for disconnection and featured the transannular addition of a vinyl lithium intermediate to an internal diacetylene group.^[9] In theory, this approach was well suited for the synthesis of **1** itself, for it would allow for the assembly of the ansa-bridged macrocycle prior to the reactive core functionality, although the feasibility of the proposed anionic transannular addition reaction, within the context of a functionally more complex macrolactone structure, was uncertain. Here, we demonstrate that the transannular cyclization strategy is effective within an ansa-bridged macrolactone substrate and implement it successfully in the first enantioselective synthesis of kedarcidin chromophore aglycon, in differentially protected form (structure **2**; MOM = methoxymethyl, TIPS = triisopropylsilyl, TES = triethylsilyl).



Our retrosynthetic analysis is outlined in Scheme 1. Final-stage operations for the synthesis of **2** were envisioned to involve C10 hydroxy group directed epoxidation of the C8–C9 olefin of the ansa-bridged bicyclo[7.3.0]dodecadienediyne **3**, selective protection of the C10 hydroxy group, and dehydration to form the C4–C5 olefin^[9, 10] steps successfully executed within our earlier, albeit simpler model system. The substrate for these operations, compound **3**, was imagined to arise by cyclization of the bromide **4**, induced by lithium–halogen exchange. Although potentially complicated by deprotonation reactions (see below), as well as competing carbonyl addition reactions, we felt that the proposed lithium–halogen exchange/transannular addition held sufficient merit to pursue the development of a synthetic route to **4**. Further, three σ bonds within the precursor **4** were targeted for disconnection: the internal diacetylene linkage (C7–C8), the lactone C–O bond, and the bromoenyne linkage (C1–C2). These could reasonably be formed in any order (six different sequences); two were investigated here. Both sequences converged upon the intermediate **5** in a proposed Glaser reaction^[11] to form the last of the three σ bonds targeted and thus to yield the macrobicyclo **4**. The paths then diverged in the ordering of the remaining two σ bond forming steps, one involving macrocyclization by lactonization, and the other by Pd-catalyzed C–C bond formation to generate the macrolactone. Both sequences were initiated by the same three starting materials (**6–8**) and incorporated an acetonide protective group within the diacetylene intermediate **7** to position the hydroxymethyl and terminal alkyne substituents in an orientation favorable for macrocyclization. Disconnection of the pyridyl ether bond within the intermediate **6**

[*] Prof. A. G. Myers, P. C. Hogan, A. R. Hurd, S. D. Goldberg
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, Massachusetts 02138 (USA)
Fax: (+1) 617-495-4976
E-mail: myers@chemistry.harvard.edu

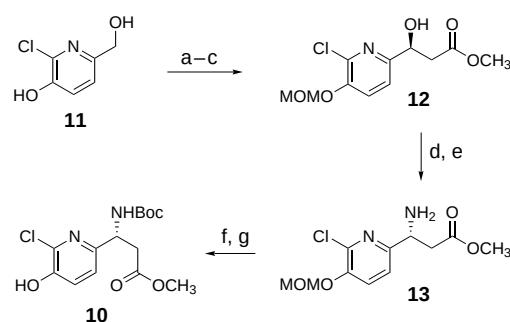
[**] Financial support from the National Institutes of Health is gratefully acknowledged. We thank Dr. Richard Staples and Mr. Andrew Haidle for the X-ray analysis of compound **20**.



Scheme 1. Retrosynthetic analysis of **2**. TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.

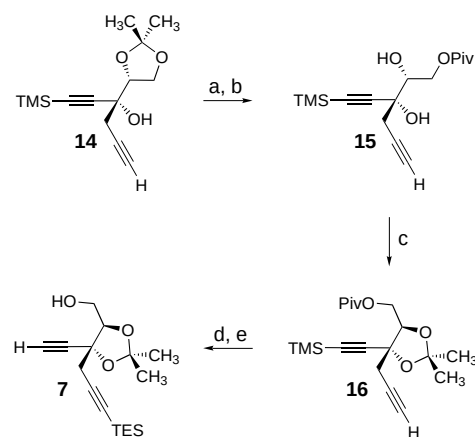
produced the two key fragments **9** and **10**. This was considered to be an advantageous feature of the approach, for it established the rather difficult pyridyl ether bond early in the sequence, rather than later, where stability issues would severely limit the options available for that transformation. Each of the four components (**7**–**10**) defined by this sequence of disconnections was prepared in multi-gram quantities. The naphthoic acid **8** was synthesized by protection of an intermediate from a prior route.^[12] The cyclic sulfate **9** was also prepared by a prior route with D-erythronolactone as starting material.^[9] The remaining components, **7** and **10**, were prepared in optically pure form, as follows.

The crystalline β -azatyrosine residue **10** was synthesized on a large scale by the highly practical and convenient Carreira–Singer aldol methodology^[13] (>30 g in one reaction, **11**^[14] $\rightarrow$ **12**, Scheme 2), adapted here for the synthesis of a β -amino acid by a subsequent Mitsunobu azidation reaction,^[15] followed by Staudinger reduction (**12** $\rightarrow$ **13**).^[16] The enantioselectivity of the asymmetric acetate aldol reaction was reproducibly high (92–94% *ee*); one recrystallization of the solid product provided optically pure material, in 90% yield. Hydrolysis of the methoxymethyl ether **13** and Boc protection of the amino group then afforded the desired β -azatyrosine fragment **10** for subsequent coupling.



Scheme 2. Synthesis of β -azatyrosine residue **10**. a) MOMCl (1.15 equiv), *i*Pr₂NEt (3.0 equiv), CH₂Cl₂, 23 °C, 81%; b) oxalyl chloride (2.0 equiv), DMSO (4.0 equiv); Et₃N (9.0 equiv), CH₂Cl₂, –78 $\rightarrow$ 0 °C, 92%; c) (S)-(–)-Carreira ligand (1.1 mol %), Ti(O*i*Pr)₄ (0.5 mol %), 3,5-di-*tert*-butylsalicylic acid (1 mol %), methyl trimethylsilyl ketene acetal (2.0 equiv), 90%, 94% *ee*; d) PPh₃ (1.2 equiv), diethyl azodicarboxylate (1.2 equiv), hydrazoic acid in toluene (1.0 N, 1.2 equiv); e) PPh₃ (1.2 equiv), H₂O (10 equiv), 23 °C, 77%; f) 12 N HCl, methanol, 23 °C; g) di-*tert*-butyl dicarbonate (1.5 equiv), Et₃N (2.2 equiv), methanol, 23 °C, 88% (two steps).

The fragment **7** was prepared from the known intermediate **14**^[17] by a five-step sequence, as shown in Scheme 3. Cleavage of the acetonide protective group and selective protection of



Scheme 3. Synthesis of alcohol **7**. a) 3 N HCl, MeOH, 23 °C 88%; b) pivaloyl chloride (1.13 equiv), pyridine, 23 °C, 87%; c) *p*-TsOH (0.2 equiv), 2,2-dimethoxypropane (10 equiv), DMF, 70 °C, 93%; d) LiHMDS (1.5 equiv), THF, –78 °C; TESCl (1.5 equiv), –78 $\rightarrow$ 23 °C 92%; e) K₂CO₃ (2 equiv), MeOH, –10 °C, 18 h, 84%. TMS = trimethylsilyl, HMDS = bis(trimethylsilyl)amide.

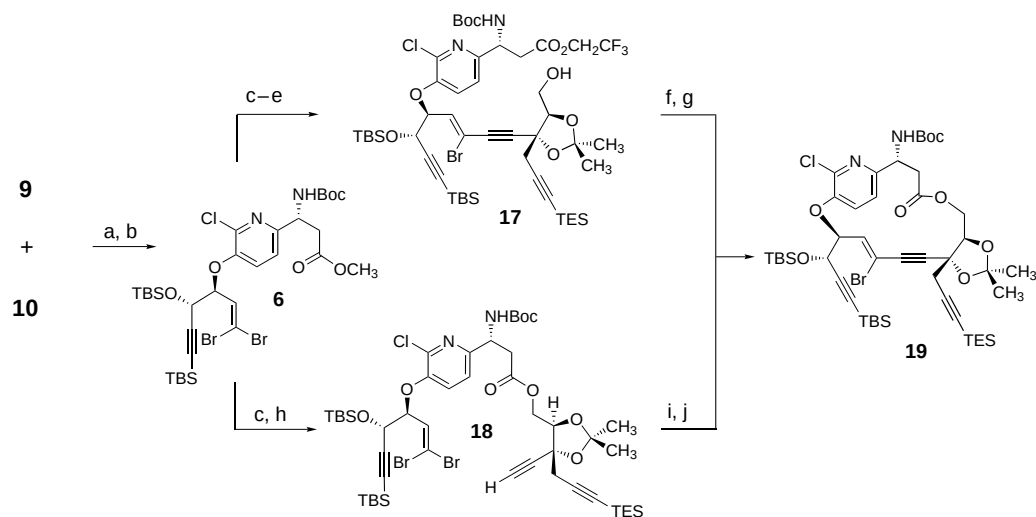
the primary hydroxy group of the resulting triol by pivaloylation provided the diol **15**. Reintroduction of an acetonide protective group, now to mask the secondary and tertiary hydroxy groups, was accomplished by using 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid in DMF at 70 °C to afford **16**. C-Deprotonation of **16** with lithium bis(trimethylsilyl)amide and trapping of the resultant acetylide anion with chlorotriethylsilane gave the corresponding differentially silylated dialkyne. Selective cleavage of the pivaloate and trimethylsilylalkyne groups then occurred upon exposure to potassium carbonate in methanol at –10 °C to produce **7** in 55% yield (over 5 steps). This sequence served to transfer the acetonide group of **14** to the contrathermodynamic position it occupies in **7**, as well as to transfer the location of the

acetylenic (silyl) protective group, necessary to allow the desired sequence of C–C bond-forming reactions.

In the first fragment-assembly step the β -azatyrosine residue **10** was coupled with the cyclic sulfate **9** to form, after sulfate hydrolysis and hydroxy protection, the pyridyl ether **6** (Scheme 4).^[9] Thus, addition of **9** to the potassium phenolate derived from **10** led to smooth and selective cleavage of the allylic sulfate ester bond (regioselectivity 9:1). Sulfate ester hydrolysis^[18] and subsequent protection of the resultant secondary alcohol with *tert*-butyldimethylsilyl chloride^[19] then afforded **6**. An apparent kinetic effect operated in the silylation reaction which served to further enrich the mixture in the desired allylic pyridyl ether regioisomer (**6**, selectivity ~20:1). The overall coupling sequence was quite efficient (73 % from **9**) and routinely provided **6** in amounts of 5–15 g.

The pyridyl ether **6** served as a common point of departure for two different sequences to the macrolactone **19** (Scheme 4). The first employed a more traditional macrolactonization reaction. For this sequence, it proved necessary to transform the methyl ester **6** into the corresponding trifluoroethyl ester prior to Pd-mediated coupling (see upper pathway). Sonogashira coupling of the resultant trifluoroethyl ester with the terminal alkyne of **7** then proceeded with selective replacement of the *trans*-bromide to furnish the bromoolefin **17** in 50–60 % yield.^[20] Bis-coupling in this reaction was a problem that, despite many efforts, was never completely suppressed. Saponification of the trifluoroethyl ester **17** (the corresponding methyl ester underwent competitive dehydrobromination) with lithium hydroperoxide cleanly afforded the corresponding hydroxy acid, which was readily cyclized by using modified Yamaguchi conditions^[21] at high dilution (ca. 0.5 mM) to form **19** in 70 % yield (efforts to cyclize **17** directly were not successful).

In an alternative and preferred sequence, ester bond formation between **6** and **7** was accomplished first, and macrocyclization was achieved in a subsequent Pd-mediated process, after a particularly useful and efficient in situ C-stannylation reaction (lower pathway, Scheme 4). Hydrolysis of the methyl ester **6** and activation of the resultant carboxylic acid allowed for smooth coupling with the primary hydroxy group of **7** to afford ester **18** in 87 % yield (2 steps). Initially, we sought to close the macrocyclic ring by direct Pd-mediated C–C bond formation within **18** (Castro–Stephens–Sonogashira coupling). Although the desired macrolactone (**19**) could be obtained in this way, yields were low (<40 %) and difficult to reproduce. Considering it likely that metalation of the hindered terminal alkyne of **18** was problematic in the coupling reaction, we investigated ways to activate this group prior to cyclization. Stannylation with the reagent diethylaminotrimethylstannane (caution! toxic), introduced by Lapert et al.^[22] and used by Stille^[23] in his initial coupling studies, proved extraordinarily successful within the multifunctional substrate **18**. Significantly, we found that the reaction could be modified by the use of toluene as solvent (as opposed to the use of neat diethylaminotrimethylstannane), and was rapid at ambient temperature with a moderate excess of reagent (3.0 equiv, ~0.1 M). Concentration of the reaction solution removed volatile by-products as well as excess reagent. Neither the alkynyl C–H nor the amido proton resonance was detected in ¹H NMR analysis of the residue. Sequential addition of ethyl ether, [Pd₂(dba)₃], and tri-2-furylphosphane^[23c] to the concentrated stannylation product then led to smooth formation of the macrolactone **19** within 12 h at 23 °C (68 % yield from **18**). A noteworthy feature of this cyclization reaction was the fact that high dilution conditions were not necessary to obtain good yields of **19**, making this the method

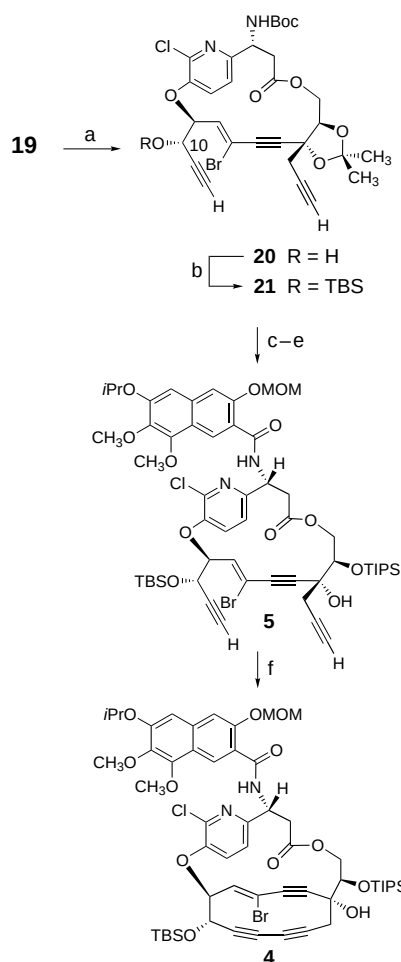


Scheme 4. Synthesis of macrolactone **19**. a) **10** (1.2 equiv), KHMDS (1.1 equiv), CH₃CN, –40 °C, 88 %; b) TBSCl (1.5 equiv), Im (6.0 equiv), DMF, 23 °C, 83 %; c) LiOH (2.0 equiv), 30 % aqueous H₂O₂/THF (1:3), 23 °C, 20 h; Na₂SO₃; d) trifluoroethanol (5.0 equiv), EDC·HCl (1.5 equiv), DMAP (0.1 equiv), CH₂Cl₂, 23 °C, 86 % (2 steps); e) **8**, (1.22 equiv), [Pd(PPh₃)₄] (0.1 equiv), CuI (0.32 equiv), Et₃N (2.2 equiv), *tert*-butyl methyl ether, 23 °C, 61 %; f) LiOH (2.0 equiv), 30 % aqueous H₂O₂/THF (1:3), 23 °C, 30 min; g) 2,4,6-Trichlorobenzoyl chloride (20 equiv), DMAP (10 equiv), Et₃N (20 equiv), toluene, 50 °C, 70 % (two steps); h) **7** (1.05 equiv), EDC·HCl (2.4 equiv), DMAP (0.1 equiv), CH₂Cl₂, 23 °C, 87 % (2 steps); i) Et₂Nsn(CH₃)₃ (3.0 equiv), toluene, 23 °C; j) [Pd₂(dba)₃] (0.1 equiv), tri-2-furylphosphane (0.8 equiv), Et₂O, 23 °C, 68 % (2 steps). Im = imidazole, dba = dibenzylideneacetone, EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, DMAP = 4-dimethylaminopyridine.

of choice for the production of **19**. We have found that the procedure described for the in situ stannylation of **18** is also effective by using other, structurally diverse terminal alkynes as substrates, and that it is tolerant of a range of functional groups (ester, amide, halide, and epoxide functional groups, among others). We recommend it as a convenient alternative to lithiation/stannylation trapping procedures. The products of both coupling–macrocyclization sequences (**19**, Scheme 4) were shown to be indistinguishable by ¹H NMR analysis.^[24] Parenthetically, we note that the acetone protective group

within **17** and **18** was critical to the success of both macrocyclization reactions; presumably it serves as a preorganizing element that favors ring closure. Substrates with alternative noncyclic protective groups cyclized more slowly, and in lower yield.

With ready access to gram-quantities of the macrolactone intermediate **19**, efforts turned toward the introduction of the naphthoamide residue, and protective group manipulations necessary to allow for Glaser cyclization to form the transannular cyclization precursor **4** (Scheme 5). Toward this end,

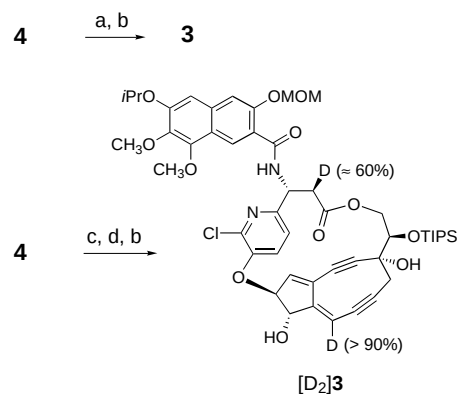


Scheme 5. Glaser cyclization to prepare the transannular cyclization precursor **4**. a) TBAF (4.5 equiv), *o*-nitrophenol (5.0 equiv), THF, 23 °C, 98%; b) TBSCl (2.0 equiv), Im (6.0 equiv), DMF, 23 °C, 97%; c) 33% TFA/CH₂Cl₂, H₂O (2.0 equiv), 23 °C; d) **7** (1.3 equiv), EDC·HCl (3.0 equiv), HOBT (1.0 equiv), Et₃N, CH₂Cl₂, 23 °C, 12 h, 81% (2 steps); e) TIPSOTf (5.0 equiv), Et₃N (15.0 equiv), CH₂Cl₂, –65 °C, 81%; f) Cu(OAc)₂ (60.0 equiv), CuI (15.0 equiv), pyridine, THF, 45 °C, 65%. TBAF=tetrabutylammonium fluoride, HOBT=1-hydroxybenzotriazole.

the macrolactone **19** was globally desilylated by using *o*-nitrophenol-buffered tetrabutylammonium fluoride in THF (98% yield)^[9] to provide the crystalline derivative **20**, whose structure was secured by single crystal X-ray analysis.^[24] After reintroduction of the TBS ether that had been cleaved in the prior step (→**21**),^[19, 24] the *tert*-butyl carbamate and acetonide groups were removed selectively by exposure of **21** to a solution of 33% trifluoroacetic acid in dichloromethane.

Concentration afforded the trifluoroacetate salt, which was treated with a solution of the naphthoic acid **8**, previously activated for coupling (EDC·HCl, HOBT), to form the corresponding naphthoic acid amide derivative in 81% yield for the two-step sequence. Selective silyl protection of the C13 secondary hydroxy group then served to fully differentiate each hydroxy group in the molecule (→**5**, 81%).^[24]

At this point a second macrocyclization reaction was achieved by employing carefully optimized, modified Eglinton conditions^[26] to afford the macrobicyclic product **4** (Scheme 5).^[24] Thus, slow addition of a solution of the macrolactone **5** in pyridine/THF (2:1) to a prewarmed (45 °C) suspension of copper(II) acetate and copper(I) iodide in pyridine/THF (2:1) produced the transannular cyclization substrate **4** in 63% yield.^[24] This product proved to be exceedingly unstable when concentrated and, in this regard, was the most unstable intermediate in the entire synthetic sequence.^[27] Although **4** could be stored as a dilute solution in toluene (–20 °C), typically, this was not done; rather, **4** was subjected to direct metalation–transannular cyclization (Scheme 6).

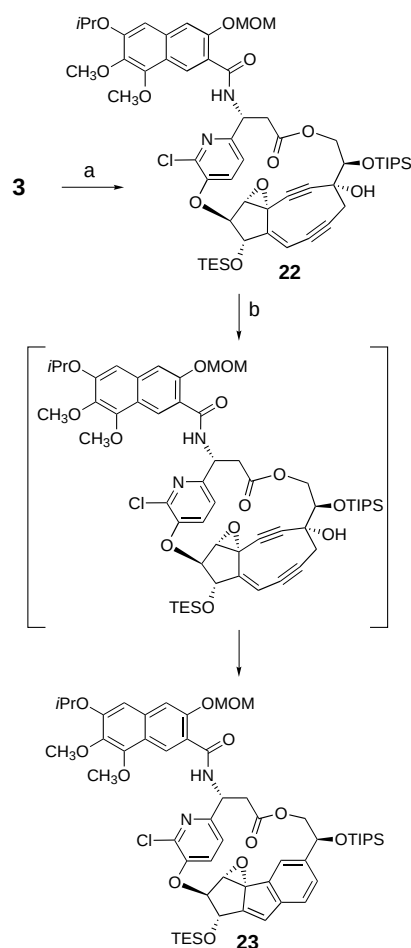


Scheme 6. Transannular cyclization and deuterium labeling. a) LiHMDS (3.5 equiv), THF, toluene, –96 °C, *t*BuLi (1.7 M, 5.0 equiv); HOAc/THF (1:10), 45–60 °C; b) Et₃N·3 HF (75 equiv), CH₃CN, 23 °C, 75%; c) CD₃OD, 23 °C; d) LiHMDS (3.5 equiv), THF, toluene, –96 °C, *t*BuLi (1.7 M, 5.0 equiv); [D₄]acetic acid/THF (1:3).

Lithium–halogen exchange within the intermediate **4** was potentially complicated by at least three competing proton-transfer events (from the secondary amide, the tertiary hydroxy group, and the α -position of the lactone). In the optimized procedure for transannular cyclization (Scheme 6), these competing processes were mitigated by prior treatment of **4** with a solution of LiHMDS in THF. After 5 min, a solution of *tert*-butyllithium in pentane was added, followed immediately (<3 s) by a quenching solution of acetic acid in THF. After cleavage of the secondary TBS ether with triethylamine trihydrofluoride and purification by flash column chromatography, the transannular cyclization product **3** was obtained, reproducibly, in 38–45% yield.^[28] Some insight into the mechanistic details of this process was gained by conducting a deuterium labeling experiment (Scheme 6). Treatment of **4** with [D₄]methanol followed by concentration from toluene (to remove methanol), dilution with THF, and sequential addition at –96 °C of solutions of LiHMDS

(3.5 equiv in THF), *tert*-butyllithium (5.0 equiv in pentanes), and [D₄]acetic acid/THF (1:3) gave rise to the isotopically labeled transannular cyclization product [D₂]-**3**, after cleavage of the TBS ether, as before. ¹H NMR analysis showed that deuterium incorporation at C8 was virtually quantitative. Interestingly, stereoselective incorporation of deuterium at the α -position of the lactone had also occurred, albeit to a lesser degree ($\approx 60\%$, stereochemistry assigned tentatively as shown on the basis of ¹H, ¹H NMR coupling constants). From this result, it is reasonable to conclude that transannular cyclization of **4** had proceeded through a polyanionic intermediate, perhaps even a tetraanion.

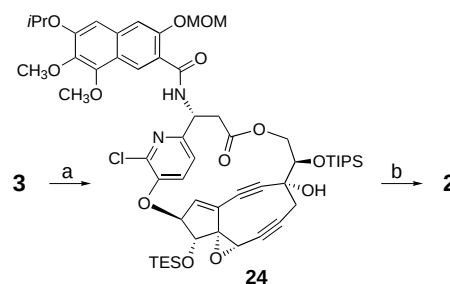
All that remained to complete the synthesis of **2** was the sequence of final stage operations initially outlined (see above; Scheme 2). However, at this point we encountered a serious problem when V-catalyzed hydroxy group directed epoxidation of **3** was found to provide the C1–C12 epoxide **22**^[24] (after selective triethylsilylation of the C10 hydroxy group), and not the desired C8–C9 epoxide (Scheme 7). This stood in contrast to our earlier findings in a model system lacking the ansa bridge, and was felt to reflect a less optimal dihedral angle for the V-catalyzed process (dihedral angles of



Scheme 7. Epoxidation of **3** to form the undesired epoxide **22**; dehydration and cycloaromatization. a) [VO(acac)₂] (0.2 equiv), *t*BuOOH (20 equiv), benzene, 23 °C; TESCl (50 equiv), Im (100 equiv), CH₂Cl₂, 23 °C; b) Martin sulfurane (10 equiv), benzene-1,4-cyclohexadiene (1:1), 23 °C, 10% (four steps). acac = acetyl acetate.

allylic alcohol estimated to be 75° in **3** and 60° in the model structure). It proved to be nontrivial to distinguish **22** from the desired epoxide **24** spectroscopically; definitive assignment of **22** was achieved in two ways. First, dehydration of the C4 tertiary hydroxy group (Martin sulfurane,^[29] benzene-1,4-cyclohexadiene (1:1)) provided the cycloaromatized elimination product **23**;^[28] its enediyne precursor was not observable. ¹H NMR analysis of **23** was consistent only with the assigned structure, and not the cycloaromatized product that would have arisen from **2**. A more definitive structural assignment was made by epoxidation/triethylsilylation of [8-D]-**3**. ¹H NMR analysis of the resultant epoxide ([8-D]-**22**) showed no vinyl proton resonance which conclusively established that epoxidation had occurred at C1–C12 of **3**. A wide range of alternative epoxidizing reagents was screened; however, most of these led to decomposition of the substrate. Notably, Jacobsen's [Mn^{III}(*R,R*)-(salen)] catalyst,^[30] Yamamoto's asymmetric vanadium catalyst,^[31] and dibutyltin oxide-*tert*-butylhydroperoxide^[32] each formed the undesired epoxide **22** as the only isolable product.

Further investigation revealed that the desired epoxide **24**^[24] was formed in preference to **22** when more hindered hydroperoxides were used in the V-catalyzed process. Both triphenylmethyl hydroperoxide^[33] and 1,1-diphenylethyl hydroperoxide^[34] gave the desired epoxide (**24**), with only a trace of **22** (Scheme 8). The use of 1,1-diphenylethyl hydroperoxide led to an increased rate of reaction, and an improved



Scheme 8. Epoxidation of **3** to afford the desired epoxide **24** and subsequent dehydration to form **2**. a) [VO(acac)₂] (0.2 equiv), CH₃CPh₂OOH (1.3 equiv), benzene, 23 °C; TESCl (50 equiv), Im (100 equiv), CH₂Cl₂, 23 °C, 32%; b) Martin sulfurane (10 equiv), benzene, 23 °C, 83%.

yield (32% vs. 20%, after in situ silylation), and was therefore preferred.^[35] With the desired epoxide **24** in hand, completion of the synthesis of **2** was achieved by dehydration in the presence of the Martin sulfurane. Synthetic **2** provided spectral data in complete accord with the assigned structure.^[24] In addition, cycloaromatization of **2**^[25] in the presence 1,4-cyclohexadiene produced the expected aromatic product^[28] which further confirms the assignment of **2**.

In conclusion, we have developed a convergent, enantioselective synthetic route to kedaridin chromophore aglycon in differentially protected form (**2**). The route is 25 steps in the longest linear sequence, with an average yield of 82% per step (overall yield 1%).

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